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OROPHARYNGEAL TULAREMIA

WALTER T. HUGHES, JR., M.D. AND JAMES N. ETTELDORF, M.D.
MEMPHIS, TENN.

WITHIN a month's time two unrelated cases of acute tonsillitis which had failed to respond to routine therapeutic measures were seen in the City of Memphis Hospitals and the patients were found to have tularemia. Stimulated by the fact that such frequently encountered symptoms resulted from a rather rare etiology, a review of our cases of tularemia over the past 15 years was undertaken. This resulted in the discovery of 3 additional cases in the pediatric age group of oropharyngeal type of tularemia which had presented in a similar manner. A brief review of tularemia and 4 illustrative cases of this type are presented to call attention to the possibility of this infection manifesting itself solely as tonsillitis.

The discovery of tularemia was heralded by the great San Francisco earthquake and fire in 1906. As a result of this tragedy and the possibility of an outbreak of bubonic plague, Dr. George W. McCoy of the U. S. Public Health Service investigated the area[1] and found a "plaguelike" disease among ground squirrels (*Citellus beecheyi*) which was characterized by pathologic lesions similar to plague, but caused by an organism somewhat different from *Pasteurella pestis*.[2] He isolated a very pleomorphic, nonmotile, gram-negative coccobacillus and named it *Pasteurella* (*Bacterium*) *tularensis* after Tulare County, California, where he found the disease.[3] Immediately after this report Wherry[4] recognized the wild rabbit as a source of the disease and the danger of transfer of the infection to man. In a matter of a few years American investigators cleverly revealed other sources of the disease, its mode of transmission, and its clinical manifestations. In 1921 Francis[5] labeled the condition "tularemia."

Today, the disease is recognized in all parts of the United States and most foreign countries. Strangely enough, tularemia is rarely seen in Tulare County, California.[6]

It has been estimated that 90 per cent of the infections in the United States follow exposure to the tissues or secretions of rabbits,[7] and that approximately 1 per cent of wild rabbits are naturally infected.[8] Burroughs and associates[9] listed 48 vertebrates known to be naturally infected with

From The Department of Pediatrics, University of Tennessee College of Medicine, and the Frank T. Tobey Memorial Children's Hospital of the City of Memphis Hospitals.

Pasteurella tularensis. Transmission by insect vectors may occur. An epidemic of the oropharyngeal type due to ingestion of contaminated water occurred in Russia in 1935.[10]

CLASSIFICATION

Tularemia is a severe systemic disease which may involve any or all organs of the body. Usually the most pronounced reaction is at the portal of entry of the infection, and this has formed a basis for classification. Six types are now recognized: (1) ulceroglandular, (2) oculoglandular (3) glandular, (4) pulmonary, (5) Typhoidal and gastrointestinal, and (6) oropharyngeal.

INCIDENCE OF OROPHARYNGEAL TULAREMIA

Since the report of the first recognized case of oropharyngeal tularemia by McGovern[11] in 1936, other case reports have been added to the literature.[12-17] Mention and general descriptions of this type have been made by others.[10, 18, 19, 20, 21, 22] Out of a total of 1,563 cases of tularemia reviewed by these authors, 68 (4.3 per cent) were of the oropharyngeal type.

Fifty-five proved cases of tularemia were seen at the City of Memphis Hospitals from 1940 through 1956. Of these, 13 patients were under 16 years of age, with 5 cases (38.5 per cent) of the oropharyngeal type.

CLINICAL MANIFESTATIONS

Tularemia must be thought of as a generalized disease, usually with signs and symptoms more pronounced at the portal of entrance of the infection. Therefore, clinical manifestations may be both local and generalized.

General manifestations consist of fever and chills, headache, vomiting and diarrhea, weakness, lethargy, coma, and eruptions of the skin;[23] there may sometimes be enlargement of the liver and spleen which is often associated with jaundice.[24]

Local manifestations in the oropharyngeal type are usually those of an acute tonsillitis with cervical lymphadenitis. The tonsils are covered with an exudate or grayish-white membrane, which may sometimes involve the posterior pharyngeal wall, the anterior faucial pillars, the base of the tongue, the soft palate, uvula, and the nasal and buccul mucosae, resembling diphtheria at times. Ulcers may be seen without a membrane. The cervical lymph nodes are enlarged, usually tender, and may suppurate. Since almost all cases result from ingestion of infected food or water, there is frequently involvement of more than one member of a family.

The incubation period is usually from 1 to 10 days.[25] The average period of incubation in 531 cases studied by Foshay was 3.30 days.[21]

The following cases serve to illustrate the clinical manifestations and course of oropharyngeal tularemia.

CASE REPORTS

CASE 1.—J. D. C., an 8-year-old Negro boy, was admitted to City of Memphis Hospitals on Dec. 9, 1956, with the presenting symptoms of fever and sore throat. One week prior to admission the child developed symptoms of an upper respiratory infection. Two days later he began to have mild, cramping abdominal pain and fever. He was taken to a physician who made a diagnosis of "viral throat" and gave the patient an "injection" along with some powdered medication. The fever persisted for one week, the abdominal

pain regressed, and soreness of the throat became more severe.

No other members of the family had been ill and the patient had had no contact with individuals with similar symptomatology.

There was no history of association with wild animals or contaminated food or water; however, the child lived in a rural area.

A physical examination revealed a well-developed, well-nourished, Negro boy with a temperature of 103.8° F., a pulse of 120 per minute, a blood pressure of 90/50 mm. Hg, and a respiratory rate of 24 per minute. He was slightly lethargic and mentally confused. The eyes and ears were not abnormal and the neck was supple. The nasal mucosa was inflamed and covered with a mucoid exudate. The pharyngeal mucosa, including the soft palate and tonsils, was beefy red; and the tonsils were covered with a dirty-gray membrane. The cervical lymph nodes were moderately enlarged, firm, and slightly tender. The heart, lungs, and abdomen were not abnormal. No lesions could be found on the skin. The deep tendon reflexes were slightly hypoactive; Kernig and Brudzinski signs were not present; there was a questionably positive Babinski sign on the right side; and the patient demonstrated a somewhat ataxic gait.

Initial laboratory studies revealed: white blood count, 11,350 per cubic millimeter (17 per cent nonsegmented neutrophils, 39 per cent segmented neutrophils, and 44 per cent lymphocytes); hemoglobin, 13.0 Gm. per cent; hematocrit, 36 volumes per cent; and normal urine. A Gram stain of the pharyngeal exudate demonstrated a few gram-positive and gram-negative cocci. The cerebrospinal fluid contained 4 white blood cells per cubic millimeter; protein was 11 mg. per cent and the sugar was 81 mg. per cent. The initial throat culture contained normal flora. Blood and spinal fluid cultures were negative. A roentgenogram of the chest was normal.

After obtaining throat and blood cultures the patient was placed on aqueous crystalline penicillin, tetracycline, and 20,000 units of diphtheria antitoxin intramuscularly, because the diagnosis of diphtheria was being considered. Four days of antibiotic therapy resulted in a normal temperature. However, three days later the fever recurred, the pharynx remained unchanged, and the ataxia was still present. A throat culture was repeated and only *Streptococcus fecalis* was recovered; blood and stool cultures again failed to reveal any pathogen; a repeat white blood cell count was 12,300 per cubic millimeter and no differential was performed; tuberculin skin test was negative; roentgenograms of the skull and chest were normal. Electrocardiogram was normal. The electroencephalogram revealed generalized abnormal activity with marked slow activity in the occipital regions with positive spikes in sleep, suggestive of the pattern seen in encephalitis.

Tests for antibodies in the blood included heterophile, typhoid, proteus X-19, brucellosis, and tularemia. Tularemia was positive in the 1:640 dilution, and the remainder were negative. The patient was then placed on streptomycin, 0.5 Gm. twice a day. (50 mg. per kilogram per day.) A dramatic response followed and the child promptly became afebrile. Streptomycin was discontiued after 7 days. The tularemia agglutination test was repeated after 1 week and was observed to be positive in a 1:640 dilution.

The patient was discharged on Jan. 5, 1957, completely asymptomatic.

CASE 2.—D. M. B., a 15-year-old Negro girl, was first admitted to City of Memphis Hospitals on Nov. 23, 1956, with the presenting complaints of sore throat, fever, and earache. She became ill on Nov. 7, 1956, with a sore throat and pain in the right ear. Her condition became worse and the fever persisted despite treatment with penicillin and sulfadiazine for 2 days. She had been unable to eat, was nauseated, and vomited. The temperature at

times had reached 105° F. Other complaints consisted of severe frontal headache, malaise, and weakness.

The patient had received diphtheria, pertussis, and smallpox immunizations at 2½ years of age, but no booster injections had been given. She had had no serious illnesses. The child lived on a farm with her parents and 7 siblings, all of whom were living and well. It is significant, perhaps, that the water supply was from a shallow well and the milk was supplied from unpasteurized sources.

Physical examination revealed a well-developed, well-nourished Negro girl who appeared acutely ill. The temperature was 102° F., pulse was 108 per minute, respiratory rate was 36 per minute, and the blood pressure was 88/60 mm. Hg.

The scalp and eyes were not abnormal. The right tympanic membrane was somewhat thickened and slightly hyperemic; no discharge was present, and there was no tenderness to pressure over the mastoid area. The left ear was not abnormal. The nasal mucosa was hyperemic. The left nostril was partially occluded by a grayish-white membrane which was hemorrhagic at its base and projected from the septum. A similar, but smaller membrane was also found in the right nostril. Tenderness to pressure was present over the sinus area. The tongue was moderately coated and white in color. The pharyngeal mucosa was diffusely hyperemic. The tonsils were enlarged, hyperemic, and covered with a grayish-white coalescent exudate. The pharyngeal reflex was present and swallowing was difficult. The neck was supple. The anterior cervical nodes were enlarged and tender bilaterally. Nodes in other areas of the body were not enlarged. The lungs and heart were not abnormal. There was some tenderness and muscle guarding of the abdomen in the upper quadrants. The extremities and skin were normal. Neurological examination revealed no abnormalities.

The hematocrit was 38 volumes per cent; white blood cell count was 8,900 per cubic milimeter, with 4 per cent nonsegmented neutrophils, 64 per cent segmented neutrophils, 19 per cent lymphocytes, and 13 per cent monocytes. VDRL test was negative. The routine urinalysis was not abnormal.

A Ponder's stain of the tonsillar exudate revealed numerous diphtheroid organisms with beading at both ends and a few cocci, which aroused some concern over the possibility of diphtheria, despite immunization. Culture of the tonsillar exudate produced *Coli aerogenes* in small numbers and normal throat flora. Culture for *C. diphtheriae* was negative. The blood culture was also nonproductive. Cultures for *Past. tularensis* were not attempted because the diagnosis was not suspected.

The patient was given penicillin and Albamycin and became afebrile in 2 days. She was discharged on the fourth hospital day asymptomatic, afebrile, and with no evidence of the tonsillar exudate or membrane.

On Dec. 2, 1956, 6 days after being discharged, the patient again experienced fever, sore throat, and headache. She had some pain in the submaxillary region and had some difficulty in swallowing. After 3 days of these symptoms she was rehospitalized. A more detailed questioning revealed she had dressed rabbits 2 months prior to onset of the present illness and she had been drinking unpasteurized milk.

The temperature was 104° F. and she was somewhat lethargic. The tonsils were enlarged, beefy red, and covered with a patchy white exudate which could easily be removed. There were several large submaxillary nodes which were tender, and there was enlargement of the nodes in the anterior and posterior cervical chains. The remainder of the physical examination revealed no abnormalities.

The white blood cell count was 12,000 per cubic millimeter with 6 per cent nonsegmented neutrophils, 37 per cent segmented neutrophils, 47 per cent lymphocytes, 2 per cent eosinophils,

and 8 per cent monocytes. The urine was normal. Routine throat culture revealed *Coli aerogenes*. Culture of the tonsillar exudate for tuberculosis was negative. The Paul-Bunnell test (heterophil agglutination) was positive in the 1:14 dilution. Agglutination studies for typhoid, paratyphoid, brucellosis, and proteus X-19 were negative. Agglutination with *Past. tularensis* was positive in the 1:320 dilution. Four days later the tularemia titer was positive in the 1:640 dilution. Culture of the tonsillar exudate for *Past. tularensis* was negative. Roentgenogram of the chest revealed no abnormalities.

On admission the patient was treated with 600,000 units of procaine penicillin intramuscularly every 12 hours, and 500 mg. of Terramycin orally every 6 hours. Symptomatic improvement was observed the following day. She remained afebrile after the third hospital day and was discharged on Dec. 13, 1956, eight days after admission, with no evidence of throat infection. Follow-up in the outpatient clinic 10 days later revealed only a few residual small cervical lymph nodes, and one month after discharge she was completely well.

CASE 3.—J. L. S., an 8-year-old Negro boy, was admitted to City of Memphis Hospitals on Dec. 27, 1946, with the presenting symptoms of sore throat and fever. Three weeks prior to admission the child had developed a sore throat followed by a high fever and these symptoms had become progressively worse. The patient had no past history of serious illnesses and had not been in contact with any contagious diseases. He had had no immunizations. He had been in recent contact with two pet rabbits.

Physical examination revealed the child to have a temperature of 105.6° F. He was fairly well developed, poorly nourished, and appeared very ill. The head, eyes, ears, and nose were not abnormal. The tonsils were greatly enlarged, hyperemic, and covered with a thick white membrane. The breath had a foul odor. There was considerable cervical lymph node enlargement and the neck was slightly stiff. There were no unusual findings in the chest, heart, abdomen, and extremities, and no skin lesions could be found.

The hemoglobin was 10 Gm. per cent and the white blood cell count was 10,350 per cubic millimeter of which 2 per cent were neutrophilic myelocytes, 1 per cent nonsegmented neutrophils, 20 per cent segmented neutrophils, and 76 per cent lymphocytes. Examination of a voided specimen of urine revealed 10 to 15 white blood cells per high-power field and a one-plus protein reaction. A Kahn test was negative. A culture of the throat produced no pathogens. A blood culture for pathogenic organisms was negative. Agglutination tests on Dec. 31, 1946, were as follows: typhoid, negative; Proteus X-19, negative; brucella, positive 1:640; and tularemia, positive 1:640. Blood cultures for *Brucella* organisms and *Past. tularensis* were negative. On Jan. 3, 1947, agglutination studies were repeated and revealed a brucella titer of 1:640 and a tularemia titer of 1:1,280. (The cross agglutination between Brucella and *Past. tularensis* will be discussed under the heading, "Agglutination Tests.")

At the time of admission the patient was given 40,000 units of diphtheria antitoxin, 20,000 units of penicillin every 3 hours, and 0.5 Gm. of sulfadiazine every 4 hours. He remained febrile on this therapy. When the diagnosis of tularemia was made on January 3, he was given streptomycin, 50 mg. intramuscularly every 3 hours, and became afebrile in 2 days. Symptomatic improvement followed. He was discharged on the fourteenth hospital day, Jan. 9, 1947.

The patient was seen one week later and had only 2 to 3 small anterior cervical nodes.

CASE 4.—D. J. F., a 4-year-old Negro girl,was admitted to City of Memphis Hospitals on Dec. 28, 1946, with the chief complaints of anorexia, sore

throat, and fever of 2 weeks' duration. This patient lived in the same house with J. L. S. (Case 3), a cousin, and had two pet rabbits.

The patient had a temperature of 101° F., weighed 40 pounds, and was well developed, but poorly nourished. The tonsils were very large and inflamed, but no membrane or exudate was present. The cervical lymph nodes were enlarged and tender. The remainder of the physical examination was not remarkable.

The hemoglobin was 8.5 Gm. per cent, and the white blood cell count was 13,250 per cubic millimeter of which 10 per cent were nonsegmented neutrophils, 62 per cent segmented neutrophils, 2 per cent eosinophils, and 26 per cent lymphocytes. The sickle cell preparation was negative. A voided urine specimen contained numerous white blood cells. Blood cultures were negative. Histoplasmin and tuberculin skin tests were negative. On January 28 the voided urine contained 10 to 15 white blood cells; on February 7 it was clear of cells. No culture of the urine was obtained. The nonprotein nitrogen was 34 mg. per cent, and an intravenous pyelogram was normal. A roentgenogram of the chest was normal. Agglutination studies for tularemia were as follows: Jan. 11, 1947, positive 1:2,560; Jan. 31, 1947, positive 1:2,560; Feb. 1, 1947, positive 1:1,280.

The patient was treated with penicillin and sulfadiazine. The hospital course was one of periods of relapsing fever for six weeks. The cervical nodes regressed in size but were still palpable at the time of discharge on Feb. 10, 1947.

The child was readmitted to the hospital on April 3, 1950, approximately 3 years after the first hospitalization. Soon after discharge in 1947 the cervical nodes were again bilaterally enlarged, suppurating and draining. It was revealed that recurrent symptoms had been occurring approximately every two weeks with intermittent fever and complaints of abdominal pain.

On examination a scar could be seen on the left side of the neck just inferior to the ear lobe where the node had drained. On the right side there was a scarred sinus tract over the body of the sternocleidomastoid muscle, with a small area of induration about it. The remainder of the physical examination was normal.

The repeat white blood cell count was 8,500 per cubic millimeter. Agglutination tests for tularemia, typhoid, brucellosis, and Proteus X-19 were negative. Cultures of the blood and of the pus from the draining lesions were negative for pyogens and tuberculosis; no culture was obtained for *Past. tularensis.* The bone marrow was cultured and found negative for pyogens, tuberculosis, and histoplasmosis; the cellular pattern was that of a slight lymphocytosis and slight eosinophilia. A tuberculin skin test was negative.

The patient was given streptomycin, 0.5 Gm. every 12 hours, and the sinus tract and small nodes on the right side were excised surgically. Microscopic study of the surgical specimen revealed a benign inclusion cyst with calcification, chronic inflammation, and a foreign-body-type reaction. Postoperatively the area healed rapidly and well, and the child remained afebrile. He was discharged asymptomatic on May 22, 1950.

In summary, each of these four patients presented with an acute tonsillitis, fever, and cervical adenitis. Three were strongly suspected of having diphtheria and none was initially suspected of having tularemia. One patient had vague symptoms of central nervous system disturbance, one had an elevated agglutination for brucellosis and one was complicated by draining sinuses from suppurated lymph nodes. Three patients were treated with streptomycin and 2 responded dramatically. The patient

with draining sinuses did not respond in the chronic stage; however, at this time the agglutination test and cultures were negative for tularemia, which might indicate a secondary infection.

D. M. B. (Case 2) was not given streptomycin because she had responded to Terramycin before the diagnosis was established.

PATHOLOGY

The only reported case in which the histopathology of the local lesion in oropharyngeal tularemia was studied is the case described by Pessin.[12] He found the ulcerative lesion of the oral mucosa to be superficially covered with a thin layer of fibrin which was mixed with cellular debris. Necrosis was limited to the superficial portion of the ulcers. Immediately beneath the fibrinous layer was a cellular response, primarily polymorphonuclear leukocytes. In deeper portions of the underlying tissue no areas of necrosis were present, and fibroblasts, histiocytes, and endothelial cells could quite definitely be distinguished. A few macrophages were encountered which, when stained by Foshay's method, revealed very small coccobacillary organisms.

In all types of tularemia there may be tiny focal necrotic areas in various stages of evolution throughout the body. These closely resemble the miliary tubercles in tuberculosis and may be found in the liver, spleen, kidneys, lungs, and other organs.

DIAGNOSIS

Oropharyngeal tularemia presents the findings of acute purulent or membranous tonsillitis with cervical lymphadenitis which must be differentiated from the following conditions: (1) Acute bacterial tonsillitis (due to *streptococcus, staphylococcus, pneumococcus, H. influenza,* etc.); (2) diphtheria, (3) infectious mononucleosis; (4) leukemia.

The following diagnostic procedures are useful in establishing the presence of a *Past. tularensis* infection:

1. *Intradermal Skin Test of Foshay.*[26]—This test, although not performed in the 4 cases presented here, is useful during the first week of the disease when agglutination tests are invariably negative. A dilute detoxified suspension of killed *Past. tularensis* organisms is injected intradermally and the reaction can be read at 48 hours. An erythematous area greater than 1 cm. is indicative of a present or past infection. Foshay[27] reports it to be positive in 92 per cent of cases in the first week. A positive reaction can be expected after the third day of illness.

2. *Culture of the Organism.—Past. tularensis* cannot be cultured on the ordinary media used for routine throat cultures. A dextrose and cystine or thioglycolate blood agar offers the best medium for culture. The organism may be cultured from the tonsillar exudate, a suppurative lymph node, sputum,[28] blood, tissue obtained by biopsy, and from the cerebrospinal fluid in cases with meningeal involvement.

Since *Past. tularensis* is capable of penetrating the intact skin,[29] many laboratory workers have become infected by handling the organism.[30] With the accuracy and reliability of the agglutination and skin tests, attempts to grow the organism on culture in most cases may impose a potential hazard to others and an unnecessary expense to the patient.

3. *Animal Inoculation.*—The most accurate and dependable method for diagnosis of tularemia is animal inoculation. One or two milliliters of blood, pus, or infected tissue is injected into the peritoneal cavity of a guinea pig or rabbit. The infected animal will succumb within a week's time and autopsy reveals the miliary "tubercles" in the liver and spleen, from which pure cultures of *Past. tularensis* can be obtained.

4. *Agglutination Tests.*—After the first week of the disease, the agglutination test is reliable and usually sufficient for diagnosis. A titer of 1:80 or over is considered diagnostic, although a progressive or rising titer is more significant.[7]

A test should also be made for *Brucella* agglutinins since there is a considerable degree of cross-agglutination with either of these infections. However, the agglutination titer of the organism causing the infection always rises highest.

The agglutination titer usually diminishes within the course of a year, but may remain positive for many years.

COMPLICATIONS

Three complications should be watched for in oropharyngeal tularemia: (1) septicemia with dissemination to other organs of the body, which occurred in 5 of the 11 cases observed by Levy;[18] (2) suppuration and drainage of regional lymph nodes; (3) retropharyngeal abscesses, which were present in 2 cases of Foshay.[21]

MORTALITY RATE

In Levy's series of 11 cases of the oropharyngeal type, one patient died, giving a mortality rate of 9 per cent. In the 6 cases seen at the City of Memphis Hospitals there were no deaths.

The over-all mortality rate in all types of tularemia averages about 4 per cent.

TREATMENT

The work of several investigators[31-36] has shown that streptomycin is remarkably effective in the treatment of all types of tularemia. In 5 cases of oropharyngeal tularemia reported by Levy[35] in which streptomycin was used, all were afebrile after 48 hours of therapy. Our 2 cases treated with streptomycin during the active infection became afebrile within 48 hours, and the drug was discontinued on the seventh day. Case 4 was first treated with streptomycin 3 years after the initial tularemic infection and did not respond. It is believed that the draining sinuses at this time were due to secondary infection, since agglutination tests and cultures for *Past. tularensis* were negative.

From the studies of Levy and the experience gained in the cases presented, it is believed that streptomycin in a dosage of 20 to 50 mg. per kilogram per day for a period of one week is sufficient.

Terramycin and Aureomycin[37] are also beneficial in the treatment of this disease, but are second in choice to streptomycin. Albamycin apparently produced a temporary response in Case 2; however, relapse occurred. There are no reports in the literature concerning the use of this drug against tularemia.

An attack of tularemia renders immunity to subsequent infection. There is no record of a second attack in man.[8] Kadull and associates[38] produced effective immunization to the disease by

the use of a phenolized suspension of *Past. tularensis.* A dose of 0.5 ml. is given subcutaneously every other day for a total of three doses. This may be of practical use in individuals who are frequently exposed to the disease, such as laboratory workers and hunters.

Isolation of the patient is not necessary since transmission from man to man does not occur.

It is elementary that avoidance of contact with infected animals, insects, water, and laboratory cultures is essential. In fact, the best prophylactic warning was given some 3,000 years ago by Moses, who wrote in his laws for purification, "Of their [hares] flesh shall ye not eat, and their carcase shall ye not touch; they are unclean to you."[39]

SUMMARY

The oropharyngeal type of tularemia is discussed and four cases are presented. The clinical manifestations are those of an acute bacterial tonsillitis with cervical lymphadenitis. The diagnosis may be made by an intradermal skin test, agglutination tests, or culture of the organism from infected tissue or fluid. The disease responds dramatically to streptomycin.

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Marlborough, Massachusetts, July 20, 1759. The Measles have been very rife in this and neighbouring Towns, whereof Numbers have died; excepting in this Town, where upwards of five Hundred have had them, from the Age of Seventy-odd to the Age of six Weeks, and not one Person died, and now all in good Health.

BOSTON WEEKLY NEWS-LETTER.

THE TIME OF PASSAGE OF THE FIRST STOOL AND URINE BY THE PREMATURE INFANT

IRVING KRAMER, M.D., AND S. NORMAN SHERRY, M.D.
BALTIMORE, MD.

SUCCESSFUL treatment of intestinal obstruction in newborn infants depends partly on early diagnosis, and partly on operative intervention before the circulation of the gut and the water and electrolyte balance of the body have been compromised. In premature infants, initial delay in feeding because of concern about their respiratory status may retard development of abdominal distention and vomiting. Since failure to pass meconium may be one of the early signs of intestinal obstruction, data have been collected on the time of passage of the first stool (and urine) in 200 normal premature infants. These data will be compared with those previously reported on the full-term infant.[1]

SUBJECTS AND METHODS

The patients were premature infants weighing less than 5½ pounds (2,500 grams) at birth at the Sinai Hospital of Baltimore from June, 1954, through August, 1955. All infants were cared for in the premature nursery. Cards were printed with space for the patient's name, birth weight, date, time of birth, date and time of passage of first stool and urine. These cards were attached to the foot of the incubators or bassinets as the patients were admitted to the nursery. Data were recorded by the nursery personnel.

RESULTS

Passage of the First Meconium Stool.—It is seen in Table I that 13 per cent of the 200 premature infants studied had passed their first stool while still in the delivery room, approximately 15 to 30 minutes after birth. Another 32 per cent passed their first stool by 12 hours of age and an additional 36 per cent in the next 12 hours. A total of 80 per cent had thus had their first stool within 24 hours after birth. In the next 24

TABLE I. TIME OF PASSAGE OF THE FIRST STOOL IN 200 PREMATURE INFANTS AS COMPARED WITH 500 NORMAL FULL-TERM INFANTS

TIME	NO.	PER CENT	CUMULATIVE PER CENT	CUMULATIVE PER CENT, FULL-TERM INFANTS
Delivery room	26	13.0	13.0	27.2
Hours				
0-12	63	31.5	44.5	69.0
12-24	71	35.5	80.0	94.0
24-48	28	14.0	94.0	99.8
Over 48 hours	12	6.0	100.0	100.0

From the Department of Pediatrics, Sinai Hospital of Baltimore, Incorporated.

hours, the cumulative percentage rose to 94 per cent.

Table II reveals that 12 premature infants went over 48 hours before having a stool. These 12 infants were

TABLE II. TIME OF APPEARANCE OF FIRST STOOL IN TWELVE NORMAL PREMATURE INFANTS WHO FIRST PASSED STOOL AFTER 48 HOURS OF AGE

HOURS	NUMBER
48-60	4
61-72	2
73-84	3
84-108	2
Over 108 hours	1*

*111 hours.

all asymptomatic and in most instances feedings had been started before they had their first stool. One of these infants passed his first stool at 111 hours of age without showing signs of intestinal obstruction. Unfortunately, no follow-up studies are available and we do not know if these infants exhibited any difficulties after leaving the hospital.

Passage of First Urine.—It is noted in Table III that 22 per cent of the premature infants had voided while still in the delivery room. Another 43 per cent passed urine by 12 hours of age. An additional 26 per cent urinated in the next 12 hours; thus a total of 91 per cent of the premature infants had urinated within 24 hours after birth. The cumulative percentage rose to 100 per cent by 48 hours.

TABLE III. TIME OF PASSAGE OF FIRST URINE IN 200 PREMATURE INFANTS AS COMPARED WITH 500 FULL-TERM INFANTS

TIME	NO.	PER CENT	CUMULATIVE PER CENT	CUMULATIVE PER CENT, FULL-TERM INFANTS
Delivery room	45	21.5	21.5	17.0
Hours				
0-12	86	43.0	64.5	67.6
12-24	52	26.0	90.5	92.4
24-48	17	9.5	100.0	99.4
Over 48 hours			100.0	100.0

DISCUSSION

Table I reveals that 94 per cent of the full-term infants passed their first stool by 24 hours after birth, while this percentage was not reached by the premature infants until 48 hours of life. These data confirm the clinical impression that there is a delay in the normal passage of the first stool by the premature infant.

There may be a marked delay or absence of the first meconium stool in newborn infants with intestinal obstruction.[2] In the absence of any symptoms, failure of a premature infant to pass stool within 24 hours of age warrants close observation. Rectal stimulation with a thermometer or an enema of 10 to 15 c.c. of normal saline may occasionally dislodge a plug and permit the free passage of the meconium. If these measures fail, development of other symptoms or failure to pass stool within the next 12 hours is an indication for further diagnostic procedures. A flat plate of the abdomen may at this time rule out mechanical intestinal obstruction if air is present throughout the intestines and there are no distended loops of bowel. Sterile water feedings may be instituted and the infant observed carefully until stool is passed.

Review of the literature reveals several references to meconium retention

in the newborn. Schwachman and associates,[3] in discussing meconium ileus, state that not all infants with difficulty in expelling meconium during the first day or two of life have meconium ileus nor will they subsequently develop pancreatic insufficiency. They describe the case of a 1-day-old infant with signs of intestinal obstruction. The consultant applied firm and gentle pressure over the baby's distended abdomen, and a large meconium plug was expelled. Although this practice was not recommended, the patient was followed for 3½ years and showed no evidence of pancreatic insufficiency. They further state that difficulty in expelling meconium may be due to congenital anomalies of the gastrointestinal tract, mechanical obstruction, defects of neurogenic nature, or weak peristaltic movements as seen in debilitated and premature infants. Bodian[4] noted several premature infants with meconium retention and symptoms of intestinal obstruction who were operated upon. None of these infants showed any structural changes to account for their clinical course. He stated, therefore, that the phenomenon was merely a sign of delayed adaptation of the intestinal tract to peristalsis in the premature infant showing itself with symptoms of functional obstruction. Santulli[5] recently reported two cases of intestinal obstruction in full-term infants. At operation, meconium casts of the large intestine were removed. These infants did well postoperatively but were later found to have Hirschsprung's disease. Rack and Crouch[6] reported a similar case in a premature infant; the follow-up on this patient is not available. Zuelzer and Wilson[7] as well as Forshall and co-workers[8] reported cases of Hirschsprung's disease in the newborn period. Most of their patients had delayed or infrequent passage of meconium associated with signs of intestinal obstruction. Those patients that came to post-mortem examination revealed absence of the myenteric plexus. Meconium retention in the newborn period suggests the diagnosis of intestinal obstruction while delayed or infrequent passage of meconium with or without signs of intestinal obstruction may be the first sign of Hirschsprung's disease.

Table III shows that 92.0 per cent of the full-term infants had voided by 24 hours after birth as compared with 91.0 per cent of the premature. Thus, as compared to the full-term infant there is no delay in the first micturition of the premature infants. All premature infants who have not voided for 24 hours should be observed closely; if there are no obvious abnormalities of the external genitalia and the kidneys do not appear to be enlarged on palpation, the clinical condition of the infant should govern further diagnostic procedures.

SUMMARY AND CONCLUSIONS

1. The times of passage of the first stool and urine were noted for 200 normal premature infants.

2. Eighty per cent of 200 premature infants had their first stool by 24 hours and 94 per cent by 48 hours after birth. This represents a delay in the passage of the first meconium stool by the normal premature infants as compared with full-term infants.

3. Ninety-one per cent of 200 premature infants had voided by 24 hours as compared to 92.0 per cent in 500

full-term infants. There is, thus, no delay in the first micturition of the normal premature infants.

4. Even in the absence of other symptoms, failure of the premature infant to pass stool by 24 hours should lead to suspicion of the possible existence of an intestinal obstruction with indicated close observation. Either earlier development of symptoms or failure to pass stool within the next 12 hours is an indication for further diagnostic procedures.

5. Similarly, close observation of all prematures who have not voided for 24 hours is indicated. The clinical condition of the infants should govern further diagnostic procedures.

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ECTOPIC AND HYPOPLASTIC PITUITARY WITH ADRENAL HYPOPLASIA

Case Report

Robert M. Ehrlich, M.D.
Toronto, Ontario

The occurrence of a hypoplastic pituitary gland in a normal infant is rare. In anencephalic monsters the pituitary has often been found to be small, and at other times apparently absent. However, careful search, including sections of the sella turcica, usually reveals small islands of pituitary cells in these cases.

Congenital hypoplasia of the pituitary and adrenals unassociated with other stigmata is exceedingly rare. During the past ten years only three cases have been reported, one with hypoplasia of the pituitary and the adrenals and the other two having absent pituitary glands with hypoplastic adrenals. All three infants died in the neonatal period. The following is a report of a patient who survived for 15 months with two separate masses of ectopic hypoplastic pituitary tissue. Both adrenals were hypoplastic.

CASE REPORT

E. L., a 15-month-old girl, had been admitted to the hospital for the first time at 2 days of age. Her mother was a 30-year-old para iii, gravida iv. Both parents were normal physically and of average intelligence. One sibling was mentally but not physically retarded. The other two children were normal in all respects.

From the Department of Pathology, Hospital for Sick Children, Toronto, Ontario, Canada.

The pregnancy had been uneventful. Labor lasted four hours and the child was delivered spontaneously, as a persistent posterior. Birth weight was 5 pounds 13 ounces. On the second day of life, twitching and periods of cyanosis were noted, and she was admitted to the Hospital for Sick Children. Physical examination at this time revealed a normally developed newborn infant, exhibiting almost continuous twitching of her extremities. Bilateral subdural taps were negative. The serum calcium was 9.2 mg. per cent and the phosphorus 8.6 mg. per cent. She was treated for tetany of the newborn. A cut-down was performed and intravenous calcium gluconate was administered. She responded well and in eight hours the twitching had ceased.

Because her appearance suggested mongolism the child was investigated by the Department of Genetics. Palmar and plantar dermal imprint patterns were intermediate between the normal and a mongoloid child.[1] Therefore, mongolism by this method was not definitely ruled out. Her convalescence was slow because of a diaper dermatitis and infection at the site of the cut-down wound. She was discharged at 25 days of age apparently well. She weighed only 6 pounds on discharge but was taking her formula well.

Following her first admission her development was retarded both mentally and physically, but she did not develop any of the classical stigmata of mongolism. At 15 months she could sit up without support.

Starting at the age of 12 months and extending over a period of 3 months she had three grand mal convulsions. With these convulsions she vomited, became unconscious and unresponsive, but recovered in a relatively short time.

Twenty-four hours before admission the child began to have a series of grand mal convulsions which were almost continuous. She vomited, became semicomatose, and did not regain consciousness. Her parents consulted their family physician, who referred the child to the hospital.

Examination revealed a very small 15-month-old child who was acutely ill and comatose. Her weight was 12 pounds. Rectal temperature was 100.8° F. Her anterior fontanel was open and full. Nevertheless she was moderately dehydrated. There was no neck stiffness. There were no other abnormal physical findings. Blood was drawn for culture and electrolyte study immediately on admission. An intravenous infusion of two-thirds 5 per cent glucose and one-third normal saline was started and she seemed to improve after about 150 ml. had been administered. This improvement, however, was not sustained, and the child died one hour after admission.

The laboratory results were as follows: blood pH, 7.11; serum sodium, 139.0 meq. per liter; serum chloride, 101.7 meq. per liter; serum potassium, 5.4 meq. per liter; serum calcium, 9.0 mg. per cent; carbon dioxide combining power, 21.9 vol. per cent; base combined bicarbonate, 9.4 meq. per liter; blood culture, no growth. No other determinations were possible because of the child's immediate death.

At post mortem the body was that of a well-proportioned child measuring 24 inches and weighing 12 pounds. (The normal is 30 inches and 23 pounds, respectively.) She had no stigmata suggesting mongolism. There were no abnormalities of the upper or lower extremities.

The heart, lungs, and kidneys appeared grossly normal and of proportionate size. The brain weighed 780 grams and revealed severe cerebral edema with cerebellar coning and notching of the temporal lobe. (The normal weight for this age is 900 to 1,000 grams.) Microscopically, the lungs showed an early degree of pulmonary edema.

The endocrine glands only were of particular interest in this autopsy.

Adrenals.—The adrenals had a combined weight of 1.2 grams. They were a light yellow color. On gross section the cortex and medulla appeared normal. Microscopically, the three layers of the cortex were evident and they were present in their usual proportions. The medulla was also normal. (Figs. 1 and 2.)

Thyroid.—The thyroid was not weighed but did not appear unduly small. Microscopically, the acini were well developed and filled with colloid. The epithelium was cuboidal and columnar in type. No parathyroid tissue was seen on the section.

Ovaries.—The ovaries were not weighed. They were small, narrow, and had a yellowish color. Microscopically, there were small follicular cysts and several small developing Graafian follicles.

Pancreas.—This organ weighed 7.5 grams. It was pale yellow in color and had a soft consisteney. The exocrine and endocrine portions revealed no histological abnormalities.

Pituitary.—When the brain was removed, the sella turcica was covered by a complete layer of dura. When this was removed, no pituitary gland was evident. However, anteriorly and inferiorly to the optic chiasma, at approximately the site of the pituitary stalk there was a small grayish-red nodule of tissue measuring approximately 2 mm. in diameter (Fig. 3). The sella turcica and the roof of the pharynx were removed in a block and decalcified. In addition, a block of tissue from the undersurface of the brain, including the optic chiasma and the hypothalamus just above the nodule

previously mentioned, was taken for histological study. Serial sections were made of both blocks. The nodule on the undersurface of the brain was found to be a collection of anterior pituitary cells in an ectopic location and underlying tissue were decalcified and the sections through them revealed a nest of cells similar to the anterior pituitary cells in the roof of the pharynx (Figs. 6 and 7). This cell nest was embedded in dense collagen fibers

Fig. 1.—A comparison of the left adrenal from E. L. with an adrenal from a 15-month-old child whose death was caused by a congenital malformation of the heart. (Hematoxylin and eosin; ×6; reduced ¼.)

Fig. 2.—Photomicrograph of the superficial layers of the adrenal cortex (E. L.) indicating the normal cellular architecture. (Hematoxylin and eosin; ×300; reduced ¼.)

(Figs. 4 and 5). Section through the middle of the block revealed a small amount of tissue posteriorly to the anterior pituitary cells, which histologically resembled the posterior part of the pituitary gland. The sella and was associated with lymphoid tissue and mucous glands. Mann stains on the pituitary gland under the optic chiasma revealed most of the cells to be chromophobe in type. There were moderate amounts of basophilic cells

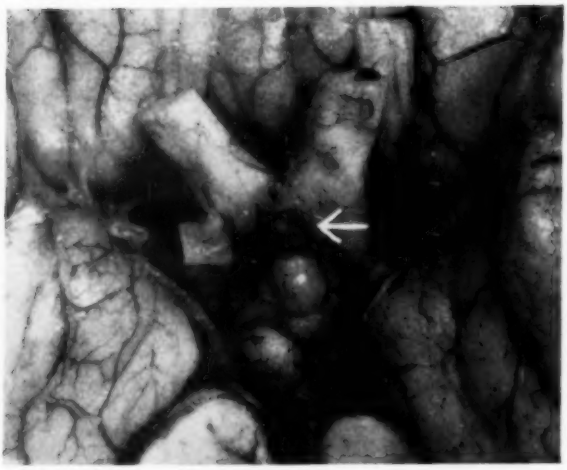

Fig. 3.—Photograph of the undersurface of the brain, the optic chiasma, and the interpeduncular space. The arrow indicates the nodule of tissue which on histologic section proved to be the anterior pituitary. Just posterior is the nodule which on section appeared to be the posterior pituitary. (×3; reduced ¼.)

Fig. 4.

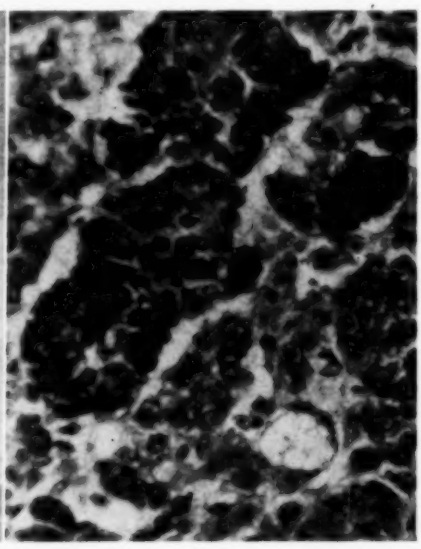

Fig. 5.

Fig. 4.—A section through the optic chiasma. The dark-staining cells comprise the anterior pituitary. Above this is the posterior portion of the gland. Below and to the right is nervous tissue which is part of the optic chiasma. (Hematoxylin and eosin; ×10; reduced 2/7.)

Fig. 5.—Photomicrograph of the nodule of anterior pituitary under the optic chiasma. The normal pituitary architecture is evident. The dark-staining cells are the acidophilic cells. (Hematoxylin and eosin; ×300; reduced 2/7.)

Fig. 6.

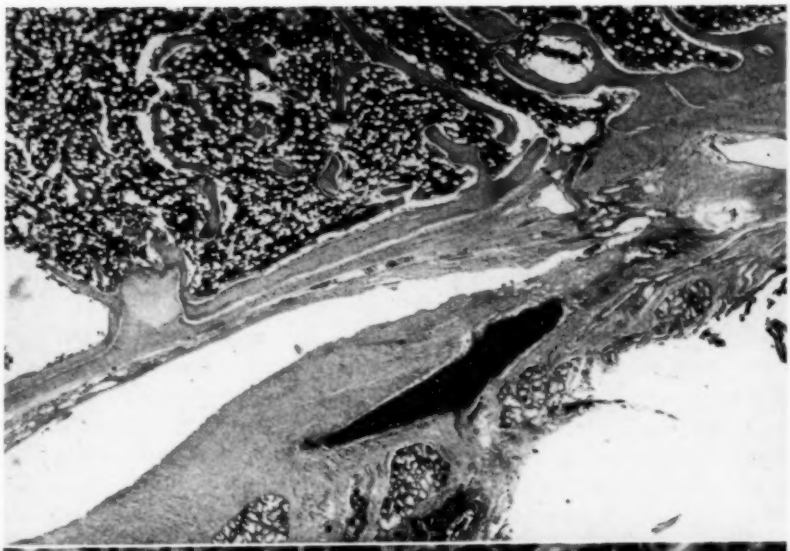

Fig. 7.

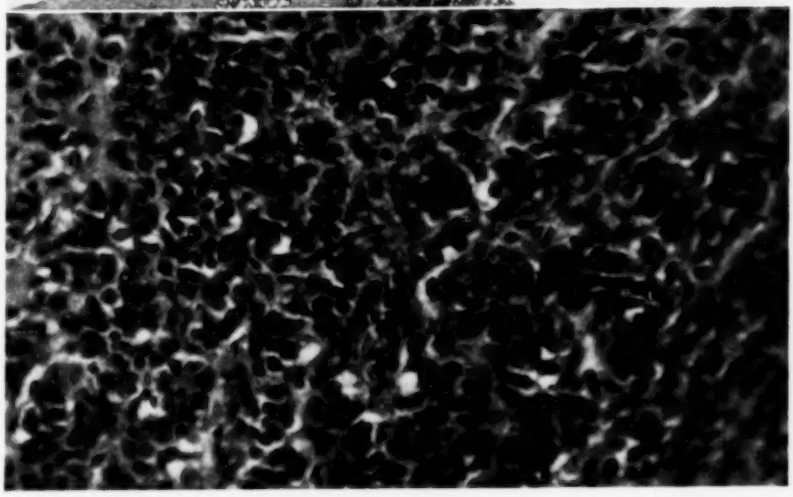

Fig. 6.—A section through the roof of the pharynx showing cancellous bone above and fibrous tissue with mucous glands below. In the fibrous tissue is a group of dark-staining cells which under higher power proved to be anterior pituitary cells. (Hematoxylin and eosin; ×10; reduced ¼.)

Fig. 7.—A photomicrograph of the cells in the roof of the pharynx. These cells lack the granularity and plumpness of the other group of cells (Fig. 5) but undoubtedly are anterior pituitary cells. (Hematoxylin and eosin; ×300; reduced ¼.)

but very few eosinophilic cells. Possibly because of decalcification, the Mann stain on the pharyngeal group of cells was not satisfactory and no conclusion could be reached as to the types of cells present. They were, however, undoubtedly anterior pituitary cells.

DISCUSSION

Congenital anomalies of the pituitary gland not associated with other defects of development are unusual. There have been three recent reports of pituitary abnormalities in newborn infants, apparently associated with changes in other endocrine glands.

Mosier[3] reported a pair of single-ovum twins who died in the neonatal period. One died at 25 hours, and at post-mortem examination hypoplastic adrenals weighing less than 1.0 gram were found, but the pituitary was not examined. The second twin died at 4 days of age. Clinically, the child was premature and was admitted to hospital because of vomiting and attacks of syncope. The vital signs were reported as normal but no blood pressure was stated. The only electrolyte studies performed showed a serum carbon dioxide of 11.0 meq. per liter, a serum chloride of 114 meq. per liter, and a serum calcium of 4.3 meq. per liter. Attempts to obtain further samples of blood were unsuccessful.

At autopsy, the pituitary was in a normal anatomical position but was very small, weighing only 0.053 gram. Microscopically, no acidophils could be seen; the cells were evenly divided between chromophobes and basophilic cells. The adrenals had a combined weight of 0.339 gram. Microscopically, the three layers of the adrenal cortex were present and in normal proportions. There was only a small amount of fetal cortex. The medulla was normal. The thyroid, pancreas, and ovaries were not remarkable. He postulated that the lack of acidophilic cells led to a lack of corticotrophin of the adrenal weight-stimulating type, with a resultant adrenal insufficiency. The acidosis present was consistent with adrenal insufficiency, but the high serum chloride was unusual.

Blizzard and Alberts[2] reported the case of a newborn infant who developed cyanosis shortly after birth. The child had underdeveloped male genitalia. Serum sodium was 142 meq. per liter and serum chloride was 114 meq. per liter. The child died within twenty-four hours with more severe cyanosis and periods of apnea. At autopsy no pituitary gland was found in the sella turcica. The adrenal glands weighed less than 1 gram. Histologically, the adrenal cortical cells were poorly formed and there was poor differentiation into layers. There was a minimal amount of fetal cortex and only a small amount of medulla. The thyroid was normal. The testes were smaller than normal and revealed an absence of interstitial cells with an increase in interstitial connective tissue. The underdevelopment of the adrenals and gonads in this case was probably due to hypopituitarism. No sections were made through the roof of the posterior pharynx and it is possible that some pituitary cell rests may have been present in that location.

Recently, Brewer[10] has published a case of absence of the anterior lobe of the pituitary gland. The pituitary stalk was present but ended in a smooth round knob. The pituitary fossa was empty. The thyroid and adrenals were small. The child was premature

and had a bilateral harelip. Histologically the pituitary stalk ended in tissue similar to the pars posterior. It was covered by pia mater. Blocks were taken through the sella and pharynx and no anterior lobe tissue could be demonstrated. The adrenals revealed poor formation of the cortical layers. The thyroid acini showed variation in size and an increase in interstitial connective tissue. Brewer thought that the absent anterior lobe was due to a failure of formation of Rathke's pouch. The bilateral harelip was not a factor since this failure of fusion occurs at a later stage of development.

Sikl[4] and Deamer and Silver[5] have reported cases of adrenal hypoplasia in newborn infants. Their patients suffered from adrenal insufficiency, but the pituitary glands were stated to be normal.

Our case presents a different problem from these others. The infant presented first with twitching in the newborn period. The serum calcium was relatively normal whereas the phosphorus was somewhat elevated, but because of the clinical picture she was treated for tetany of the newborn and responded well. After this initial episode the child was retarded mentally and physically, developed convulsions, and died in status epileticus with cerebral edema at 15 months of age. The case probably represents a pituitary dwarf due to ectopic and hypoplastic pituitary tissue.

Pituitary dwarfs usually develop fairly normally during the first year of life and then begin to lag behind. Often, no evidence of deficiency of thyroid, adrenal, or gonadal function can be detected early. Lack of gonadotrophic hormone is usually the first deficit noted and becomes manifest as the patient grows older by retarded genital development and sexual maturation. Thyroid deficiencies may also be present but are not as evident as in cretinism. Pituitary dwarfs often suffer hypoglycemic attacks which are probably indicative of a lack of growth hormone or adrenal insufficiency. According to Wilkins,[6] occurrence of true electrolyte upsets such as may be seen in other forms of adrenal insufficiency is unusual in pituitary dwarfs. Therefore, as is well known, it can be seen that the diagnosis of pituitary dwarfism is difficult in early childhood. If the hypopituitarism is due to a tumor, signs of increased intracranial pressure may help in the diagnosis.

In our case the pituitary gland was small, and histologically there was an apparent deficiency of the acidophilic cells, although some were present. These cells are thought to be the source of somatotrophin and this deficiency might explain the retarded growth. Some ACTH, TSH, and FSH were probably being produced because some development of the adrenal, thyroid, and ovary did occur. The child's appearance (at post mortem) did not suggest deficiency of any of these hormones.

The development of convulsions at 1 year of age remains unexplained but there are two possibilities. The seizures may have been due to the coincidental development of a convulsive disorder. However, it seems more likely that they were due to hypoglycemia. Unfortunately no blood sugar determination was obtained before the child died. Regardless of their cause, it seems probable that this added stress on the homeostatic mechanisms of the body was too much for the child and

she succumbed. The normal sodium potassium and chloride found in the serum on admission would suggest that the adrenals were functioning normally, but as previously stated the Addisonian electrolyte picture is not seen in pituitary dwarfs. The metabolic acidosis present is consistent with acute adrenal insufficiency or may be due to the excess release of acid metabolites from muscle, which can occur in status epilepticus. This hypothesis of partial pituitary insufficiency would explain the clinical picture.

The anatomic findings could be explained by postulating that during intrauterine life the outgrowth from the primitive buccal cavity (Rathke's pouch) which forms the anterior lobe of the pituitary became separated into two distinct masses. The one mass migrated further dorsally than usual, leaving the sella empty. The other mass remained in close proximity to the roof of the posterior pharynx. This pharyngeal remnant has been called the "pharyngeal hypophysis."

SUMMARY

A case is reported of a 15-month-old child who exhibited two masses of anterior pituitary tissue, both of which appeared hypoplastic. In addition, there was a relative and absolute lack of eosinophilic cells. It is postulated that the child suffered from partial pituitary insufficiency.

I would like to thank Dr. J. D. Bailey and Dr. W. L. Donohue for their kind assistance in the preparation of this paper.

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THE NEPHROTIC SYNDROME ASSOCIATED WITH RENAL VEIN THROMBOSIS

Report of Case in an Infant

Burton Feinerman, M.D., Edmund C. Burke, M.D., and Robert C. Bahn, M.D.
Rochester, Minn.

THE association of the nephrotic syndrome and thrombosis of the renal veins rarely has been reported in the pediatric literature. The purpose of this paper is to review previous reports and to present a case recently encountered at the Mayo Clinic.

Rayer[1] in 1840 described two patients with thrombosis of the renal veins and with the nephrotic syndrome. One patient, 50 years of age, had generalized edema, proteinuria, and recurrent lumbar pain. Necropsy revealed that the kidneys were enlarged and soft and both renal veins were thrombosed. The other patient, a young girl, had edema and advanced proteinuria at the time of death. Necropsy revealed enlargement of the kidneys and thrombosis of the renal veins.

Subsequent to 1840 the literature contained many reports of the association of the nephrotic syndrome with thrombosis of the renal veins in adults. Pollak and associates[2] have made an excellent summary of these cases; however, very few reports appear in the literature of this syndrome occurring in infants and children. Vidal[3] in 1854 described the case of a 12-year-old boy and Neu[4] in 1922 reported the case of a 12-year-old girl; in 1939 Derow and associates[5] reported the case of a 15-year-old boy, and in 1950 Miller and his associates[6] presented the case of an 18-year-old boy (Table I). These four patients had essentially the same clinical features with massive edema, lumbar pain, and proteinuria.

Table I. Summary of Findings in Cases Reported in the Literature

Author	Patient: Age (yr.) and Sex	Clinical Features	Duration of Symptoms Prior to Death	Laboratory Findings
Vidal[3]	12 M	Diarrhea, anasarca, lumbar pain, tenderness in abdomen	17 days	Proteinuria
Neu[4]	12 F	Weakness, nausea, edema, oliguria	40 days	Proteinuria
Derow and associates[5]	12 M	Pain and tenderness in lumbar regions, edema	16 months	Hypoalbuminemia, hyperlipemia, proteinuria
Miller and associates[6]	18 M	Pain in abdomen, edema	2 months	Hypoalbuminemia, hyperlipemia, proteinuria

From the Section of Pediatrics and Section of Pathologic Anatomy, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

In 1956 Kark[7] summarized the clinical manifestations of 16 cases of thrombosis of the renal veins and the nephrotic syndrome occurring in adults. All patients had edema and proteinuria; 9 had severe pain in the loins, 7 had thrombosis in the veins of the legs, 7 had hematuria, 4 had pulmonary infarctions, and 2 had severe abdominal pain. Kark[7] also reviewed the histologic features of kidneys seen in patients having this clinical syndrome. The basement membranes were thickened and appeared as "wire loops," and the capillary lumina in the glomeruli were narrowed; dilatation and atrophy were seen in the tubules, and edema and fibrosis were noted in the interstitium.

CASE REPORT

An 18-month-old boy was admitted to the Mayo Clinic because of generalized edema and gangrene of the right great toe.

Five months prior to admission the boy had measles complicated with pneumonitis. Twelve days after the onset of measles, his parents noted swelling around his eyes. This persisted until 2 months prior to his admission when it also was noted that the abdomen and left leg were swelling. The right leg felt cold and shortly afterward the right great toe became dusky and finally black. His family physician noted that the boy had an elevated blood pressure and albuminuria; urea measured 56 mg. per 100 c.c. of blood. The boy was treated with Apresoline, reserpine, heparin, Dicumarol, antibiotics, a 10-day course of ACTH, and salt-poor albumin without any improvement. Paracentesis was performed 1 month prior to his admission to the clinic and 1,300 c.c. of fluid was removed.

On admission, the child appeared extremely pale, with swelling around the eyes, ascites, and marked edema of both lower extremities. The blood pressure was 150/100 mm. of Hg, pulse 86, respirations 24, temperature 100° F. The right great toe was gangrenous and the right foot felt warmer than the left. Pulses in the lower extremities were not felt. Examination of the fundi revealed generalized narrowing of the arterioles. Retinitis was not present and the optic disks and maculae were normal. No other abnormalities were noted on physical examination.

Laboratory findings on admission were as follows: urinalysis showed a specific gravity of urine of 1.026, albuminuria grade 4+, frequent hyaline and granular casts, and 6 leukocytes per high-power field; studies of the blood showed hemoglobin, 9.8 Gm. per 100 c.c.; 2,600,000 erythrocytes and 9,000 leukocytes per cubic millimeter with a normal differential count, sedimentation rate of 125 mm. in the first hour (Westergren method); urea, 56 mg. per 100 c.c.; cholesterol, 250 mg. per 100 c.c. of plasma; and 134 meq. of sodium, 5 meq. of potassium, 105 meq. of chlorides, and a carbon dioxide combining power of 15 meq. per liter of serum. Electrophoresis of the protein revealed the following values: total protein, 4.20 Gm. per 100 c.c. of serum; albumin (19.3 per cent) 0.81 Gm.; alpha-1 globulin (5.7 per cent) 0.24 Gm.; alpha-2 globulin (45.8 per cent) 1.92 Gm.; beta globulin (17.9 per cent) 0.75 Gm.; and gamma globulin (11.3 per cent) 0.48 Gm. A roentgenogram of the thorax did not show evidence of any abnormality. Results of a study of the kidneys, ureters, and bladder were negative. A culture of ascitic fluid was also negative.

The patient was given a course of adrenocorticotropin (75 mg. a day in divided doses) for 8 days, but diuresis was minimal. Response to Rolicton was likewise unsatisfactory. Two weeks after admission moderate respiratory distress developed and moist râles were heard at the bases of both lungs. No friction rub was noted.

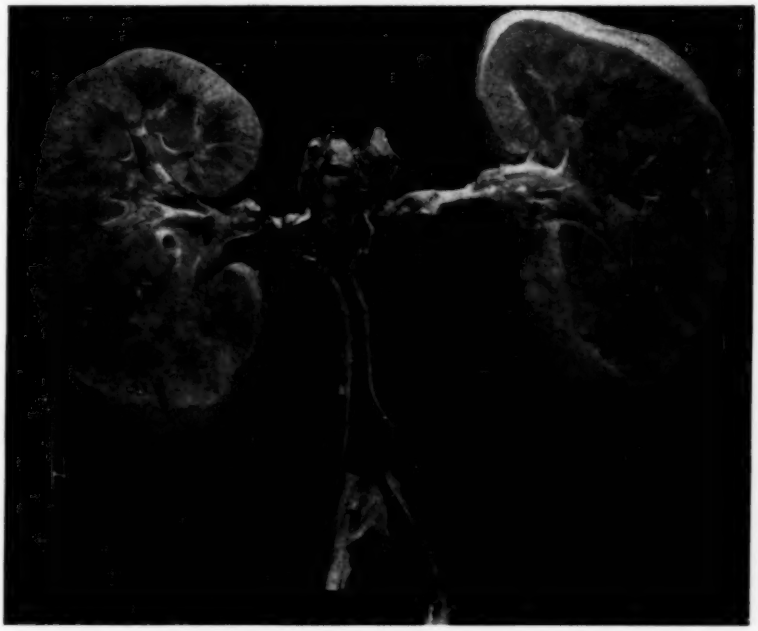


Fig. 1.—Inferior vena cava occluded by an organized thrombus which extended from the iliofemoral veins to the entrance of the hepatic veins.

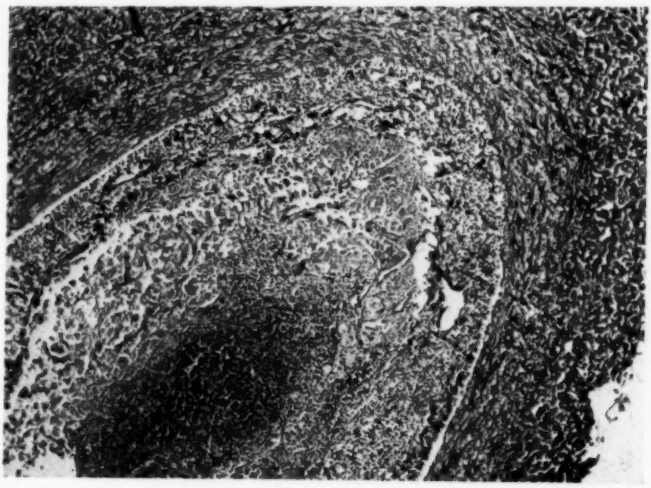


Fig. 2.—Organized thrombus in the inferior vena cava (hematoxylin and eosin; ×50).

Antibiotics were administered in large doses and the patient was placed in an oxygen tent. Three weeks after admission the patient had a generalized convulsion which lasted several minutes. At this time the chemical constituents of the blood were as follows: urea, 192 mg. per 100 c.c. of blood; and 155 meq. of sodium, 4.9 meq. of potassium, 131 meq. of chlorides, and a carbon dioxide combining power of 13 meq. per liter of serum. Progressive impairment developed in the circulation of the right foot, and gangrene now involved the distal phalanges of the third, fourth, and fifth toes of the

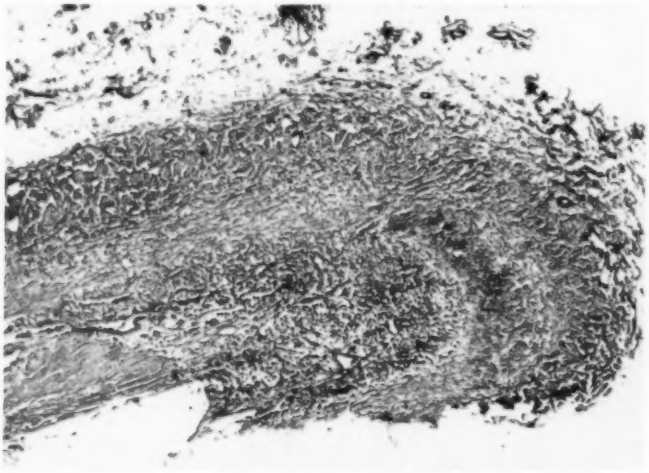


Fig. 3.—Organized thrombus in left renal vein (hematoxylin and eosin; ×50).

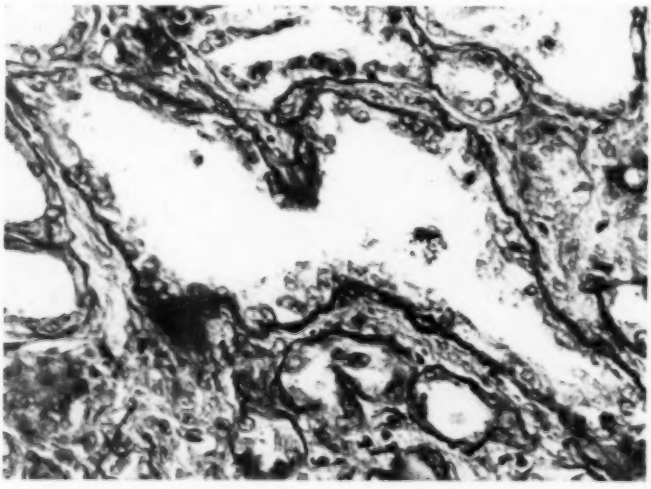


Fig. 4.—Thickening of the basement membrane of the renal tubules (periodic acid-Schiff-hematoxylin stain; ×360).

right foot. The urinary output became greatly reduced and the patient's temperature was subnormal the week prior to death. Paracentesis failed to relieve respiratory distress. Anuria developed and the patient died one month after admission.

The pertinent observations recorded at necropsy were as follows: The inferior vena cava was occluded by an organized thrombus which extended from the iliofemoral veins to the level of the entrance of the hepatic veins (Figs. 1 and 2). The left and right renal veins were occluded by organized thrombi (Fig. 3). Both kidneys were pale and enlarged. The renal cortices measured 0.5 to 0.8 cm. in thickness and yellow streaks were seen on the cut surface. The appearance of the cut surface of the renal medulla was not unusual.

Both kidneys exhibited similar histologic alterations. The stroma of many glomeruli was prominent and the basement membrane of the renal tubules appeared to be thickened (Fig. 4). Some proximal convoluted tubules were dilated. Their lumina contained a few erythrocytes, precipitated protein, cellular fragments, and amorphous debris while the lining epithelial cells, when stained with Sudan IV, showed many lipid droplets.

The epithelium of other proximal convoluted tubules contained colloid droplets which were easily visualized by Mallory-Heidenhain (Fig. 5) and phosphotungstic acid hematoxylin stains. The interstitial tissues of the cortex and medulla were prominent and showed foci of lymphocytes and macrophages.

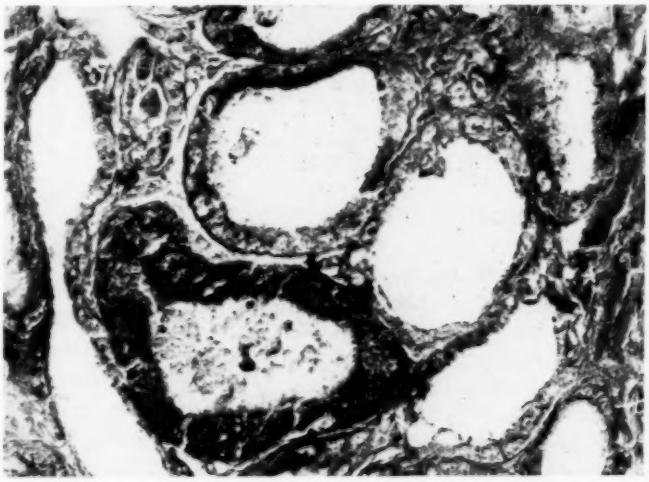


Fig. 5.—Colloid droplets in the epithelium of proximal convoluted tubules (Mallory-Heidenhain stain; ×450).

The main right branch of the pulmonary artery contained a fairly large thrombus. There were congestion of the lungs and an area of hemorrhagic infarction in the lower lobe of the right lung.

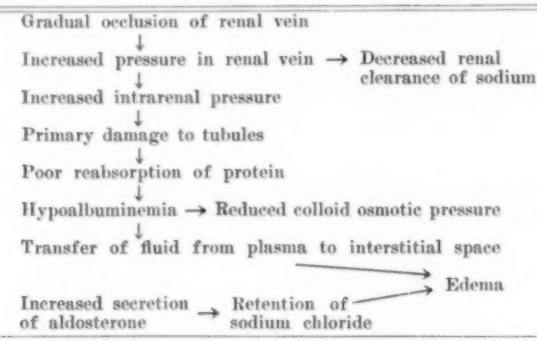
COMMENT

The clinical course that this patient presented was unique. Glomerulonephritis, lupus erythematosus, diabetes mellitus, lipoid nephrosis, and amyloidosis had to be considered in the differential diagnosis as possible causes of the nephrotic syndrome. The absence of palpable peripheral pulses and the

presence of gangrene of the toes suggested a thrombotic phenomenon.

The possible mechanism for the production of edema with thrombosis of the renal veins is summarized in Table II.

Table II. Possible Mechanism Producing Edema and Thrombosis of Renal Veins


Gradual occlusion of renal vein
Increased pressure in renal vein
Decreased renal clearance of sodium
Increased intrarenal pressure
Primary damage to tubules
Poor reabsorption of protein
Hypoalbuminemia
Reduced colloid osmotic pressure
Transfer of fluid from plasma to interstitial space
Edema
Increased secretion of aldosterone
Retention of sodium chloride

In retrospect, anticoagulant therapy might have been helpful in this case. Heparin has been used with varying degrees of success in adults who have had thrombosis of the renal veins and the nephrotic syndrome,[2, 7] and experimental evidence also shows that heparin may be useful in management of the nephrotic syndrome. In the experimental production of nephrotic syndrome in laboratory animals heparin reduces lipemia,[8] may have an anticomplement effect interfering with antigen-antibody action,[9] and reduces the mortality rate in nephrotic rats as compared to controls or rats that have received cortisone, collagenase, and hyaluronidase.[10] It is hoped that increasing awareness of the possibility of thrombosis of the renal veins as producing the nephrotic syndrome may result in more successful management of this exceedingly serious condition. In regard to the genesis of thrombosis of the renal veins we can, as yet, only speculate. Thrombosis may be septic in origin or may possibly be due to so-called sludging of the blood in a debilitated patient.

SUMMARY

An 18-month-old boy was brought to the Mayo Clinic because of gangrene of one toe and generalized edema. The clinical course and pathologic findings indicated the presence of thrombosis of the renal veins and the nephrotic syndrome. Necropsy revealed thrombi in the inferior vena cava and both renal veins. Only four cases of the nephrotic syndrome and thrombosis of the renal veins occurring in children have been reported in the literature heretofore and these are reviewed briefly. A theory as to the possible mechanism for the pathogenesis of edema has been developed. However, the cause of thrombosis of the renal veins remains unknown.

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We hear from Durham, New-Hampshire, that the wife of one Mr. Joseph Reynolds of that place, was lately delivered of a child, which had five fingers and a thumb on each hand, and six toes on each foot; which was the 4th she had born after that manner.

BOSTON EVENING POST, October 6, 1760.

SEPTICEMIA OF THE NEWBORN DUE TO LISTERIA MONOCYTOGENES

A Case Report and Review of the Literature

Joseph Wiener, Captain, MC, AUS*

HISTORY

LISTERIA MONOCYTOGENES was first isolated and studied as a new species, *Bacterium monocytogenes*, by Murray, Webb, and Swann[1] in 1924, from an epizootic among guinea pigs and rabbits in their laboratory at Cambridge. The organism called *Bacterium hepatis* in 1911 by Hülphers[2] was undoubtedly *Listeria monocytogenes*. The same organism was recovered by Pirie[3] from four wild gerbilles (*Tatera lobengulae*) in South Africa in 1925. Struck by the necrosis in the liver, he called the organism *Listerella hepatolytica*, in honor of Lord Lister. When he became acquainted with the work of the English investigators, the name *Listerella monocytogenes* was adopted. The generic name Listerella was disallowed by the Third International Congress for Microbiology in 1939 on the grounds that Jahn had already used the name for a myxetozoan in 1906. Pirie,[4] in 1940, subsequently proposed that the name Listeria be substituted.

The first recognized isolation of Listeria from a human being was recorded by Nyfeldt[5] in 1929. He recovered the organism from the blood stream of a patient with infectious mononucleosis. Listeria was first recognized as the cause of disease in domestic animals by Gill[6] in 1931, when he isolated it from sheep in New Zealand. He gave the name "circling disease" to the encephalitis which it produced. Listeria meningitis was first observed in the United States by Burn[7] in 1934. Gibson[8] reported the first proved case of listeriosis in Great Britain in 1935, but it was not until 1937 that complete identification of the organism was made by Webb and Barber.[9] However, cases of meningitis ascribed to diphtheroids which were undoubtedly due to *Listeria monocytogenes* were reported by Atkinson[10] in 1917, Dick[11] in 1920, Dumont and Cotoni[12] in 1921, Kessel and Romanoff[13] in 1930, and Tesdal[14] in 1934.

Since these initial publications, *Listeria monocytogenes* has been isolated from at least 27 animal species and man in 26 countries spread over five continents.[15] Listeriosis has been reviewed by Julianelle,[16] Kaplan,[17] Girard and Murray,[18] and Murray.[15, 19] Seeliger and Linzenmeir[20] have reviewed 147 cases of Listeria infections in man. Finegold, Bradley, Campbell, and Greenberg[21] have reviewed 39 cases of Listeria meningitis. *Listeria monocytogenes*, as a cause of sepsis in the neonatal period, has attracted little attention in the

*Chief, Laboratory Service, United States Army Hospital, Fort Riley, Kansas. Present address: Mallory Institute of Pathology, Boston City Hospital, Boston, Mass.

English literature. It has, however, attracted considerable attention in the European literature. Potel and others[22-26] have collected 40 cases in the neonatal period around Halle, Germany. These infants suffered from an acute septicemic disease, fatal in a large number of cases, which the authors called "granulomatosis infantiseptica." Miliary granulomata with necrosis characterized the disease. The lesions were found particularly in the liver, spleen, adrenal glands, lymph nodes, lungs, and brain. Ten similar cases, all fatal, were reported in Prague by Patocka and Benda[27] in 1953. We have recently observed a similar case at this hospital. The paucity of articles detailing the pathologic anatomy prompts this report.

CASE REPORT

A male infant, I. V. Y., was born four weeks prematurely on July 1, 1956, at the United States Army Hospital, Fort Riley, Kansas.

The mother was a 19-year-old Okinawan, gravida i, para 0. The husband was a white Sergeant First Class. Her prenatal course was entirely unremarkable. No febrile illnesses were reported. Upon admission to hospital the membranes were intact. The membranes ruptured 13½ hours after admission. The first stage of labor was completed 6 hours later. The duration of the second stage was 27 minutes. Delivery was accomplished by low forceps under saddle block anesthesia. The duration of the third stage was 8 minutes, the placenta being removed manually. Examination of the placenta revealed the membranes to be stained bright green. No odor was detected, however. Unfortunately, the placenta was not submitted for pathologic examination. The mother's post-partum course was unremarkable. No elevations were recorded in the temperature chart.

At birth, the infant weighed 2,264 grams. The temperature was 96.2° F. The infant responded slowly and was placed in an incubator, with added oxygen. The temperature was noted to be 103° F. three and one-half hours after delivery. During the second day of life the temperature remained elevated, fluctuating between 102.4° and 104.6° F. The pyrexia responded slightly to tap water sponges. Examination during the day revealed a normal premature infant, without an apparent cause for the fever. Empirically, penicillin, 200,000 units, and streptomycin, 0.125 Gm., intramuscularly, every 12 hours, were ordered. As there was no response to therapy, a lumbar puncture was performed. The tap was traumatic, delivering bloody cerebrospinal fluid. The fluid was cultured. Blood cultures were also drawn.

The hemoglobin at this time was 18.0 grams per cent. The red blood count was 6,200,000 per cubic millimeter. The white blood count was 37,950 per cubic millimeter, with a differential count as follows: 42 per cent polymorphonuclear leukocytes, 6 per cent juveniles, 7 per cent bands, 31 per cent lymphocytes, and 14 per cent monocytes. There were two normoblasts per 100 white cells. No organisms were noted on the smears made from the spinal fluid sediment.

The fever persisted throughout the next morning. The respirations became shallow and labored terminally. Cyanosis appeared. The infant expired on the morning of July 3, 36 hours after birth.

Necropsy was performed two hours after death. The body measured 32.0 cm. crown-rump, and 47.0 cm. crown-heel. The significant findings on gross examination were limited to the lungs, liver, and brain. The external surfaces of both lungs were bluish-white, smooth and glistening. On

section, the parenchyma was subcrepitant and slightly nodular to palpation. The liver was slightly enlarged, weighing 120 grams. The surface and substance of both lobes were studded with grayish-white circular nodules which were not elevated or palpable. The nodules measured up to 0.1 cm. in diameter.

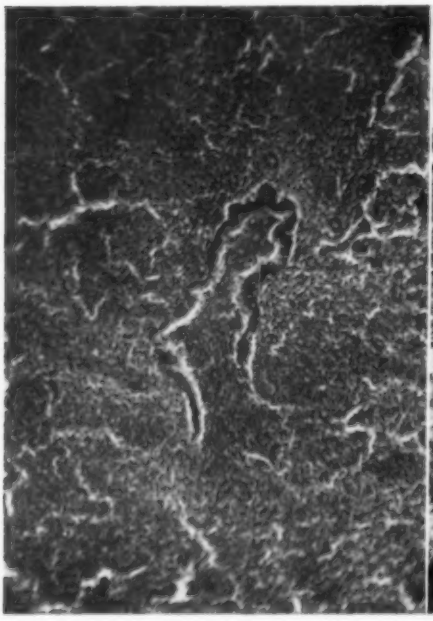

Fig. 1.

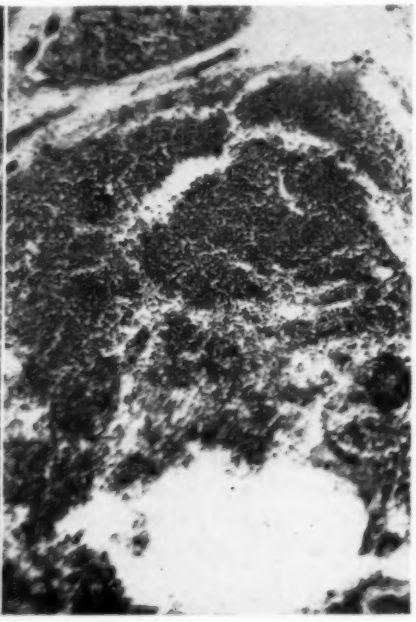

Fig. 2.

Fig. 1.—Right lower lobe. The bronchiolar lumen is filled with exudate. There is necrosis of a portion of the wall. The surrounding pneumonia is well marked. (Hematoxylin and eosin; ×100; reduced 1/5.)

Fig. 2.—Paratracheal lymph node. A subcapsular zone of necrosis is present. (Hematoxylin and eosin; ×100; reduced 1/5.)

The brain was also enlarged, weighing 385 grams. There were patches of greenish-yellow exudate in the subarachnoid space about both temporal poles. Small amounts of clotted blood were noted in the subarachnoid space about the superior surface of the cerebellum and within the ventricles.

The significant findings on microscopic examination were limited to lungs, lymph nodes, intestine, liver, adrenal glands, and brain. Sections of all five pulmonary lobes revealed an essentially similar process, perhaps more severe in both lower lobes. Many of the bronchioles contained a dense exudate of polymorphonuclear leukocytes and large monocytes. There was necrosis of the bronchiolar walls, with confluence of the exudate within the lumina with a similar exudate in the alveoli (Fig. 1). Red blood cells were also noted in the alveolar spaces. The alveolar septa were thickened and infiltrated by similar inflammatory cells. One of the paratracheal lymph nodes revealed a large subcapsular zone of necrosis (Fig. 2). Nuclear detritus, polymorphonuclear leukocytes, and large

monocytes were discerned in this area. Sections of spleen revealed extramedullary hematopoiesis and focal areas of congestion. No areas of necrosis were found. Two lymphoid nodules within the jejunum also exhibited necrosis (Fig. 3). A similar area of necrosis was noted within the submucosa of the colon. Scattered diffusely through the liver were miliary-like foci of necrosis which were in various stages of development (Figs. 4 and 5). Polymorphonuclear leukocytes, large monocytes, and nuclear debris were once more present in these regions. Similar prominent about the temporal poles, the sites of the gross lesions. The exudate consisted of polymorphonuclear leukocytes, large monocytes, and red blood cells once again (Fig. 9). Areas of necrosis were also noted. The vessels were congested. Similar inflammatory cells were noted within their walls. Small areas of subarachnoid hemorrhage were noted about the cerebellum. Perivascular cuffing by monocytes and lymphocytes was seen within the white matter (Figs. 10 and 11). The occasional vessel was surrounded by polymorphonuclear leukocytes. The

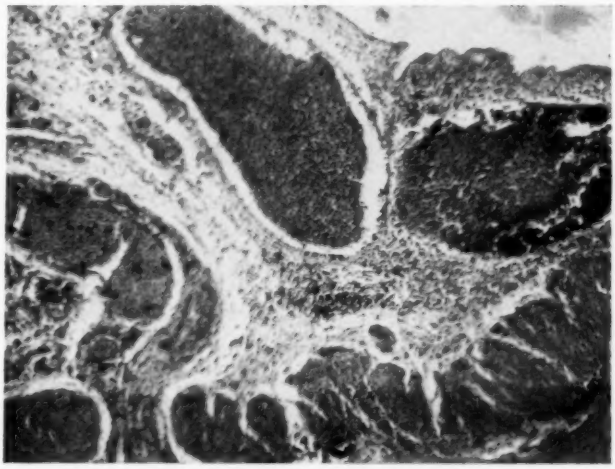

Fig. 3.—Jejunum. There is marked necrosis of the lymphoid nodules in the serosa. (Hematoxylin and eosin; ×100; reduced ⅙.)

cells were present in the portal tracts. The walls of the hepatic arteries were acidophilic and the endothelial cells lining the lumina were swollen. The sinusoids were congested. Large foci of extramedullary hematopoiesis were scattered throughout. Sections of adrenal glands revealed similar foci of necrosis within the cortex and medulla (Figs. 6 and 7). Sections of brain revealed a dense exudate within the subarachnoid space about the cerebrum, cerebellum, and brain stem (Fig. 8). The exudate was most choroid plexuses were densely infiltrated by similar inflammatory cells (Fig. 12). Areas of necrosis were prominent. The ventricles contained small amounts of exudate and blood. The ependyma and subjacent tissue of the ventricles also contained similar inflammatory cells.

At autopsy, cultures were taken from the right lower lobe and left lower lobe, spleen, heart blood, cerebrospinal fluid, and meningeal exudate. All cultures, except spleen, revealed a diphtheroid-like organism. A similar bacillus was isolated from

Fig. 4. Fig. 5.

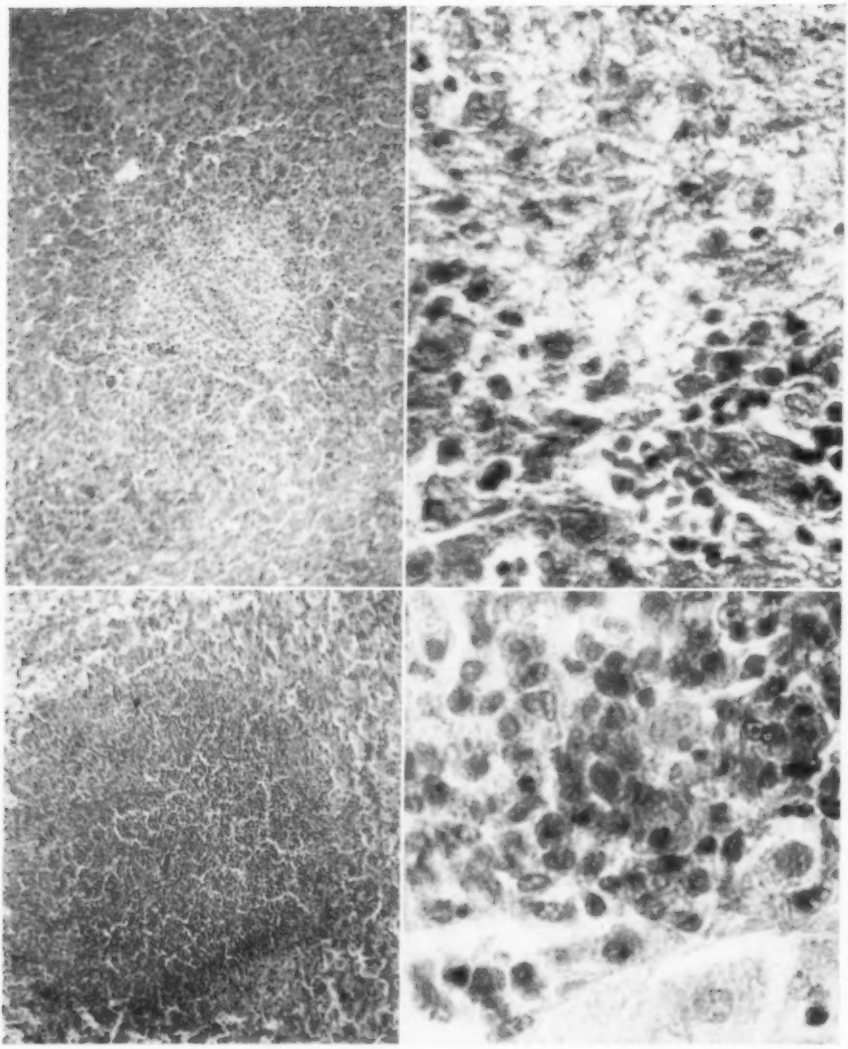

Fig. 6. Fig. 7.

Fig. 4.—Liver. There is a central area of necrosis. Surrounding foci of extramedullary hematopoiesis are noted. (Hematoxylin and eosin; ×100; reduced ⅙.)

Fig. 5.—Liver. There is a slight mononuclear infiltrate within the area of necrosis. The reticulin fibers are prominent. There is a peripheral narrow rim of normal parenchyma. (Hematoxylin and eosin; ×750; reduced ⅙.)

Fig. 6.—Right adrenal gland. There is a prominent cortical area of necrosis. The inflammatory infiltrate is heavy. (Hematoxylin and eosin; ×100; reduced ⅙.)

Fig. 7.—Right adrenal gland. The area of necrosis is infiltrated by polymorphonuclear leukocytes and large monocytes. There is a thin rim of normal cortex present. (Hematoxylin and eosin; ×750; reduced ⅙.)

Fig. 8.

Fig. 9.

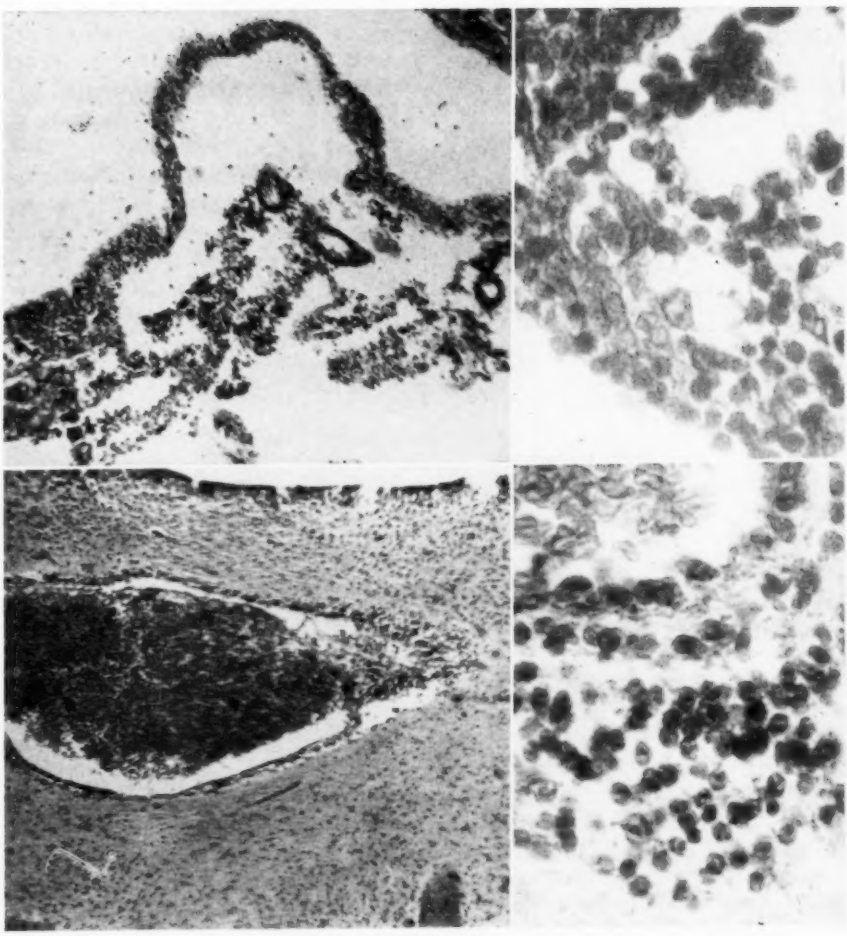

Fig. 10.

Fig. 11.

Fig. 8.—Brain. The leptomeninges contain a cellular exudate. (Hematoxylin and eosin; ×100; reduced ⅓.)

Fig. 9.—Brain. Large monocytes are a prominent constituent of the exudate within the subarachnoid space. (Hematoxylin and eosin; ×750; reduced ⅓.)

Fig. 10.—Brain. There is perivascular cuffing in the region of the lateral ventricle. (Hematoxylin and eosin; ×100; reduced ⅓.)

Fig. 11.—Brain. Large monocytes are a prominent constituent of the perivascular infiltrate. (Hematoxylin and eosin; ×750; reduced ⅓.)

the ante-mortem blood and spinal fluid cultures. Because of the unusual nature of the case, cultures were forwarded to the Fifth U. S. Army Medical Laboratory. The organism was identified by the Bacteriology Section as *Listeria monocytogenes*. Confirmation of identification was made at the Walter Reed Army Institute of Research, the Third U. S. Army Medical Laboratory and Fitzsimons Army Hospital.

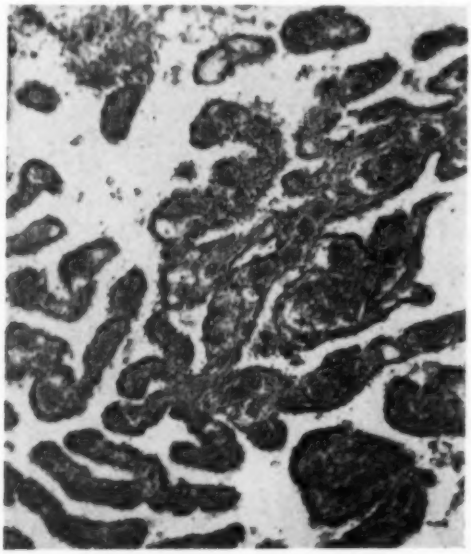

Fig. 12.—Brain. There is a suppurative choroiditis within the lateral ventricle. (Hematoxylin and eosin; ×100; reduced 1/5.)

Post-partum vaginal cultures of the mother revealed *Listeria monocytogenes*. Similar organisms were not found in the throat cultures taken from the parents. Gram stains of the tissue sections revealed gram-positive rods within the necrotic foci.

REVIEW OF THE LITERATURE

In addition to the cases described in Germany and Czechoslovakia, at least 16 cases of listeriosis have been described in the neonatal period. These have been described by Burn[28] (3 cases), Kapsenberg[29] (1 case), Van Driest[30] (1 case), Slooff[31] (1 case), Beute, Meyler, and Sirks[32] (1 case), Stoot[33] (1 case), Line and Cherry[34] (2 cases), Line and Appleton[35] (1 case), Portero and Despirito[36] (1 case), Selinger and Becker[37] (1 case), Johnston, Morton, Wong, and Roy[38] (2 cases), and Mathieu, Young, Mennillo, and Sherwood[39] (1 case). The cases consisted of sepsis and/or meningitis. Though the series is too small to be statistically significant, only one case occurred in a Negro infant. There were five premature infants. The patients varied in age from 3 hours to 3 weeks. Three cases,[28] all fatal, were reported before the era of specific therapy. Of the 13 cases reported since that time, 6 infants died, including one patient of Line and Cherry[34] who developed

obstructive hydrocephalus. This infant expired at 9 months of age of pulmonary complications following a Torkildsen procedure. Two patients[30, 39] have residual hydrocephalus.

Among the symptoms elicited from the parents are fever, irritability, lethargy, rapid or labored respirations, cyanosis, anorexia, diarrhea, vomiting, and jaundice. Physical examination may be entirely unremarkable. Among the signs recorded are pyrexia, drowsiness, air hunger, and cyanosis which may be peripheral. The head may be retracted. The anterior fontanel may be soft or tense. The throat and eardrums may appear hyperemic. Examination of the heart reveals a tachycardia. The respirations may be rapid and shallow or irregular and slow. Dullness and râles have been described. Significant physical findings recorded on neurological examination are nystagmus, a stiff back, and Brudzinski's and Kernig's signs. The reflexes may be irregular, absent, or hyperactive.

The white blood count is elevated, ranging from 11,900 to 38,600 white blood cells per cubic millimeter. Neutrophils predominate. There may be a shift to the left. Urinalysis may be normal, or may reveal albuminuria varying in degree from slight to moderate. The cerebrospinal fluid has been described as clear, cloudy, xanthochromic, or greenish in color. The pressure may be normal or increased. The cerebrospinal fluid sugar is generally decreased. The spinal fluid protein is markedly elevated. The chlorides are variable. The cell count is markedly elevated. Polymorphonuclear leukocytes predominate early. Lymphocytes predominate later in the course of infection. In this respect, Listeria meningitis simulates tuberculous meningitis. Stained smears (Gram's method) of the spinal fluid may reveal the organism.

EPIDEMIOLOGY

Although the incidence of human listeriosis indicates a low degree of communicability, two cases of Burn,[28] five cases of Atkinson,[10] and the two cases of Line and Cherry[34] suggest that listeriosis is capable of assuming epidemic proportions when favorable circumstances are present. Little information is available concerning the reservoir of infection or mode of transmission. Attempts have frequently been made to relate human cases to contact with domestic animals or use of their unsterilized products. Odegaard, Ronnarg, and Henricksen[40] have recorded a case transmitted from sheep. However, evidence supporting the frequent infection of man from animals is lacking. In 1950, Morris and Norman[41] isolated Listeria from ferrets at the Army Graduate School of Medicine. The animals were not afflicted apparently with the disease. This finding raises the question of healthy carriers. Patocka and Benda[27] stated that some of the mothers in their cases experienced minor influenza-like illnesses at different periods preceding delivery. Bacteriological studies on the mothers and relatives post partum revealed no Listeria. However, complement fixation tests between the mothers' sera and homologous or heterologous Listeria antigens were often positive in high titers. In only one case was the febrile illness associated with labor.

The avenue of Listeria infection is equally obscure. Throat cultures in parents and siblings have not yielded Listeria. *Listeria monocytogenes* has been isolated both ante partum and post partum from the mothers' vaginas. Potel has stated that in his cases of "granulomatosis infantiseptica" the meconium always yields positive cultures, due to the swallowing of infected amniotic fluid. He believes that the severe pulmonary lesions are due to inhalation of the heavily infected liquor. This view is supported by a case of Johnston, Morton, Wong, and Roy.[38] Experimentally, Murray, Webb, and Swann[1] succeeded in infecting three baby rabbits by feeding the animals cultures of *Listeria monocytogenes* in place of drinking water. On the other hand, Patocka and Benda[27] state that filtrable forms of the microorganism may exist which pass through intact organs and affect the growth and development of sensitive embryonic tissue. The distribution of brain lesions suggests the possibility of spread by way of the vascular sheaths, canals, and meninges.[18]

DIAGNOSIS

The clinical features of listeriosis are not so well defined that a diagnosis can be made on the basis of the history, symptoms, and signs. The actual diagnosis depends upon the alertness of the bacteriologist. The diagnosis can be lost in the laboratory when the bacteriologist is not alert to the possible etiology. In this regard, the strain isolated from this case report was sent out as a monthly survey specimen to 14 laboratories. Only five laboratories successfully identified the organism as *Listeria monocytogenes.*

Cultures should be made from the blood, cerebrospinal fluid, meconium, urine, placenta, milk, lochia, pus, and exudates according to the case. Blood cultures may be sterile, even in cases of septicemia. This finding should not exclude listeriosis. At autopsy, cultures should be taken from all the viscera. The medulla oblongata should not be neglected. The technique of Gray, Stafseth, and Thorp[42] should be used. Since the agglutination titer fades rapidly after recovery it cannot serve reliably for late diagnosis. A rising or high titer (over 1:200) is significant.

BACTERIOLOGY

The organisms, on primary isolation, appear as short gram-positive rods usually in pairs or short chains. They tend to form palisades and their slightly curved or "V" shape resembles the diphtheroids in morphology. Growth is usually sparse on plain agar medium but is usually luxuriant on media enriched with glucose or body fluids. Blood agar plates are satisfactory. On blood agar, a narrow zone of beta hemolysis is usually evident within 24 to 48 hours of incubation. The colonies are small and round, measuring 1 to 2 mm. in diameter. Unless care is taken, the organism may be mistaken for a beta hemolytic streptococcus. *Listeria monocytogenes* may occasionally be confused with *Hemophilus influenzae* due to the ease with which it is decolorized with Gram stains.[37] Listeria, differing from the nonmotile diphtheroids, are sluggishly motile. They exhibit a characteristic "tumbling" or spiral movement. The use

of semisolid media for motility determination will enable recognition of this characteristic. The bacteriologist will then be aware that the organism is not a diphtheroid or streptococcus. Motility is enhanced when the organism is incubated at room temperature, but is readily noted in specimens incubated at 37° C. On carbohydrates, acid without gas is usually produced within 24 hours from glucose, dextrin, maltose, mannose, rhamnose, trehalose, salicin, and levulose. Variable results are obtained with glycerol, lactose, sucrose, and starch. Gelatin is not liquefied. Indole and hydrogen sulfide are not formed.[43]

The characteristics outlined are sufficient to establish the diagnosis of Listeria infection. They are well within the resources of every laboratory. In addition, but certainly not necessary for identification, are two animal tests that are specific for the microorganism. The first of these tests was described by Anton[44] in 1934. He observed that the organism, when instilled into the conjunctival sac, incites a severe conjunctivitis and later a keratitis in guinea pigs. At about the same time, Morris and Julianelle,[45] and later Julianelle and Pons[46] described a similar test in rabbits and guinea pigs. The latter found that this reaction is absolutely specific for *Listeria monocytogenes*.

A second characteristic manifestation is the monocytosis produced in the blood of naturally and experimentally infected rabbits. This was first noted by Murray, Webb, and Swann.[1] The monocytosis may rise as high as 20,000 per cubic millimeter. The dosage of the inoculum is important, since volumes as small as 0.25 c.c. of a 24-hour glucose broth culture of some strains are fatal.[47] Stanley,[48] in 1949, reported that a chloroform and ether soluble lipid extracted from *Listeria monocytogenes* was responsible for the monocytosis. This monocytosis-producing agent is liberated chiefly in the liver. It is neither antigenic nor toxic.

There are four recognized serotypes established by Paterson[49] based on the "H" antigen of Listeria. The "O" antigens are distinctive for Types three and four, but identical in Types one and two. Types one and four are world-wide in distribution. Type three seems to occur only in Denmark and East Germany. Type two occurs only in Great Britain. The majority of Type four biotypes ferment melicitose while the majority of Type one biotypes do not ferment melicitose.[15]

SPECIFIC TREATMENT

Specific therapy was first utilized in the treatment of listeriosis in 1939. Porter and Hale[50] used sulfanilamide to treat a child in Iowa with Listeria meningitis. In the same year Porzecanski and DeBaygorria[51] successfully used Prontosil 27 to treat a 19-year-old Uruguayan patient with Listeria meningitis. There are discrepancies in the estimation of sensitivity of *Listeria monocytogenes* to various antibiotics. This may be due, at least in part, to the fact that various authors have reported results in utilizing the tube-dilution method, while others have used the more rapid, but less accurate, antibiotic-impregnated sensitivity disks. Good results have been reported with many antibiotics. Stanley[52] isolated a strain which was

quite resistant to penicillin. Similar results have been reported by Foley, Epstein, and Lee.[53] The strain isolated by Stanley was found by Gray, Stafseth, and Thorp[54] to acquire resistance to streptomycin rapidly. Weller and Janeway[55] state that Listeria strains are sensitive both in vivo and in vitro to chlortetracycline, somewhat less sensitive to oxytetracycline, and relatively resistant to penicillin and streptomycin. Norman, Longfellow, and Levin[56] state that chlortetracycline is more effective than chloramphenicol. Finegold, Bradley, Campbell, and Greenberg[21] recommend that cases of Listeria meningitis be treated with chlortetracycline or oxytetracycline, preferably by the intravenous route for the first few days, and sulfadiazine and/or streptomycin. Mathieu, Young, Mennillo, and Sherwood[39] state that treatment must be continued until the patient is clinically well and two successive cerebrospinal fluids are entirely normal. These same authors consider the use of enzymes intrathecally to lyse the meningeal exudate and thus prevent the serious complication of obstructive hydrocephalus.

SUMMARY

A case of septicemia in the neonatal period due to *Listeria monocytogenes* is reported. The pathologic anatomy is described and the literature on this subject is reviewed. The epidemiology is discussed. Bacteriological diagnosis is emphasized and specific treatment is presented.

I am indebted to Albert Leibovitz, Lieutenant Colonel, MSC, Chief, Bacteriology Section, Fifth U. S. Army Medical Laboratory, who originally identified the organism as *Listeria monocytogenes*, for his assistance in the preparation of this article.

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URINARY CALCULUS DISEASE AMONG ISRAELI IMMIGRANT AND ARAB CHILDREN

DAVID LEVY, M.D., AND WALTER FALK, M.D.
HAIFA, ISRAEL

SURPRISINGLY little has been written on urinary calculosis in childhood during the past decade, although it is one of the chief problems of pediatric urology. Only rarely have articles appeared in a pediatric journal and much that was previously accepted is being questioned. In recent years careful studies have been carried out on various animal species under different pathological conditions.

Little has been done on the influence of race or ethnic origin and heredity, and no conclusive reports have been published on the influence of climatic and other environmental conditions. This report deals with thirty-one cases of urinary lithiasis in children coming from different environments, belonging to distinctly different ethnic groups, and observed by the same medical personnel.

DESCRIPTION OF CLINICAL MATERIAL

The thirty-one cases of urinary lithiasis reported here were observed at the Rambam Government Hospital in Haifa, from 1949 up to the end of 1956. They represent all the cases of urolithiasis diagnosed among all the patients hospitalized for various illnesses during this period of time. Since no elective factor was involved in the assessment of these cases, this group of patients may be considered a random sample and therefore suitable for statistical evaluation. The essential data pertaining to these thirty-one patients are presented in Table I.

As seen in Table I the age of the patients at the time of their hospitalization ranged between 2 months and 13 years. Twenty were males and eleven, females (Table II). Twenty of the thirty-one patients had a single stone each, four had multiple stones in one kidney, six had stones in both kidneys, while one had multiple stones in both kidneys and both ureters. In ten cases a pyelolithotomy was performed, in four cases a ureterolithotomy, and in three a cystotomy, in one case the diseased kidney was removed. Of the remaining thirteen cases, spontaneous expulsion took place in five, four patients were not operated upon in this hospital, and in four the calculi were revealed at autopsy. One of the children operated upon died. He had suffered from prolonged uremia and the autopsy revealed agenesis of the right kidney, ulcerative colitis, and purulent pyelitis. Urine cultures were sterile in twenty-three cases; among the rest *Pseudomonas aeruginosa* was found in three cases (4, 6, 8), *Bacillus coli* in three cases (3, 9, 29) and *Bacillus proteus* in two cases (18, 24).

From the Rambam Government Hospital, Pediatric Department B.

TABLE I. PERTINENT DATA OF 31 PATIENTS WITH UROLITHIASIS

NO.	AGE IN MO.	SEX	ETHNIC GROUP	LOCALIZATION OF STONE	PRESENTING SYMPTOM	PRINCIPAL DIAGNOSES
1	42	F	Ashken.	Left kidney	Abdominal pains	Nephrolithiasis, left
2	60	M	Eastern	Urethra	Spontaneous expulsion	Repeated spontaneous expulsion of stones
3	48	M	Yemenite	Bladder	Dysuria	Bladder calculus
4	48	M	Eastern	2 stones in each kidney	Edema of face and legs	Calculi in both kidneys; pyelitis; ascariasis
5	30	F	Arab	Left kidney	Albumin and leucocytes in urine	Rickets; kyphoscoliosis due to rickets; dwarfism; ascariasis; nephrolithiasis, left
6	48	M	Eastern	Bladder	Accidental on x-ray examination	Celiac disease; malnutrition; status postparalytic poliomyelitis; bladder calculus
7	48	F	Yemenite	Right kidney	Albuminuria; pyrexia	Nephrolithiasis; hydronephrosis; otitis media
8	54	M	Arab	Urethra	Dysuria	Urethral stone
9	36	F	Eastern	Left kidney	Dysuria	Pyelonephritis; nephrolithiasis, left
10	60	M	Eastern	Right kidney	Albumin and leucocytes in urine	Nephrolithiasis, right; tonsillitis
11	30	M	Yemenite	Left ureter	Anuria	Agenesis of right kidney; left ureterolithiasis; anuria; uremia; ulcerative colitis
12	36	F	Ashken.	Left kidney	Abdominal pains	Spontaneous expulsion of urinary stone; hydronephrosis of left kidney
13	30	M	Arab	Left ureter	Hematuria	Ureterolithiasis, left
14	18	M	Yemenite	Urethra	Stone found in meatus urethra	Hydronephrosis of right kidney; poliomyelitis
15	15	M	Eastern	Urethra	Spontaneous expulsion	Varicella; urethrolithiasis
16	22	F	Eastern	Right ureter	Pyuria	Ureterolithiasis; gastroenteritis
17	132	M	Eastern	Left ureter	Hematuria	Ureterolithiasis; pyodermia
18	120	F	Arab	Both kidneys and ureters	Hematuria	Second and third degree burns; multiple stones in urinary tract
19	108	M	Ashken.	Right kidney	Abdominal pains	Acute appendicitis; renal stone
20	132	M	Arab	Left kidney	Abdominal pains	Multiple stones (5) in left kidney
21	132	M	Arab	Right ureter	Abdominal pains	Status postparalytic poliomyelitis; ureterolithiasis
22	120	M	Arab	Urethra	Abdominal pains; dysuria	Spontaneous expulsion of urethral calculus

TABLE I—CONT'D

NO.	IN AGE MO.	SEX	ETHNIC GROUP	LOCALIZATION OF STONE	PRESENTING SYMPTOM	PRINCIPAL DIAGNOSES
23	120	F	Eastern	Both kidneys; right, 3 stones	Hematuria	Bilateral nephrolithiasis; hydronephrosis
24	144	M	Arab	Left kidney 4 stones	Hematuria	Left nephrolithiasis; hydronephrosis with no kidney tissue left; nephrectomy
25	156	M	Ashken.	Right kidney 2 stones	Abdominal pains	Right nephrolithiasis
26	2	F	Eastern	Stones in both kidneys	P.M. finding*	Bronchopneumonia; malnutrition; bilateral nephrolithiasis
27	6	F	Yemenite	Stones in both kidneys	P.M. finding*	Pertussis; bronchopneumonia; gastroenteritis; malnutrition; bilateral nephrolithiasis
28	2½	M	Yemenite	Stones in both kidneys	P.M. finding*	Bronchopneumonia; malnutrition; bilateral nephrolithiasis
29	2	F	Eastern	Stones in both kidneys	Pyelitis; P.M. finding	Gastroenteritis; pyelitis; malnutrition; bilateral nephrolithiasis
30	25	M	Arab	Left kidney	Hematuria	Nephrolithiasis, left
31	144	M	Arab	Right kidney 4 stones	Abdominal pains; bulging of abdominal wall	Nephrolithiasis, right; hydronephrosis, right

Eastern—Eastern Jews ethnic group, coming from Asian and African Arab countries.
Yemenite—Yemenite Jews ethnic group, coming from Yemen and Aden.
Ashken.—Ashkenazic Jews ethnic group, coming from Eastern and Central European countries.
Arab—A child coming from the Arab minority group in Israel.
P.M.—Post-mortem examination of body.
*Not diagnosed during life; no specific or suggesting symptoms have been diagnosed during hospitalization.

TABLE II. NUMBER OF CHILDREN WITH UROLITHIASIS BY AGE AND SEX

AGE IN YEARS	NUMBER OF PATIENTS	PER CENT OF TOTAL NUMBER	MALE	FEMALE
Under 1 year	4	13	1	3
1-2	3	10	2	1
2-3	6	19	3	3
3-4	5	16	3	2
4-5	3	10	3	–
8-9	1	3	1	–
9-10	3	10	1	2
10-11	3	10	3	–
11-12	2	6	2	–
12-13	1	3	1	–
Total	31	100	20	11

The patients have been grouped according to their ethnic origin. Five ethnic groups are recognized in Israel: the Sepharadie Jews from the Balkan countries, Turkey, Spain, and Portugal; the Ashkenazic Jews from all the eastern and middle European countries; the Eastern Jews from the Arab

countries in Asia and Africa (Iraq, Iran, Egypt, Morocco, Tripoli, Algeria, Tunisia, and others); the Yemenite Jews, originating in Yemen and Aden; and the Israeli Arab group. The frequency distribution of the cases according to their ethnic origin is shown in Table III.

TABLE III. DISTRIBUTION OF CASES OF UROLITHIASIS ACCORDING TO ETHNIC ORIGIN

ETHNIC GROUP	NUMBER OF CASES	PER CENT OF ALL CASES
Ashkenazic Jews	4	13
Eastern Jews	11	36
Yemenite Jews	6	19
Arabs	10	32
Sepharadic	nil	–
Total	31	100

All the Jewish patients and/or their parents were new immigrants. Most of them have lived for varying periods in immigrant camps. This implies primitive living quarters, mostly tents and barracks, and subsistence on a poor, monotonous diet. Some of the children came directly from these camps, while the rest were hospitalized for only relatively short periods of time after leaving them. The Arab children came mostly from the impoverished elements. Their standards of living and social development were low.

ANALYSIS OF CLINICAL MATERIAL

Incidence.—The incidence of pediatric urolithiasis in children is calculated in various ways by different authors. Hager and Magath[1] consider incidence in percentage of pediatric urolithiasis cases in series including patients of all ages. They reported that fifteen out of 1,808 renal stones, seven out of 813 ureteral, and eleven out of 674 vesical calculi were in children, an over-all incidence of 1.63 per cent. Lett[2] reported fifty-one cases in children among a group of 2,781 patients with urolithiasis admitted to the London Hospital during a period of thirty years. Joly[3] found three pediatric patients in 636 patients with calculi treated at the St. Peter Hospital in London between 1915 and 1924. Thomson,[4] on the other hand, stated that 25 per cent of the urinary calculi in a Canton hospital were in children, and in Thailand[5] reported an incidence of 22 per cent in children under 11 years of age. Campbell[5] found sixty-seven cases of urinary calculosis in a series of 15,919 autopsies in children under 15 years of age, an incidence of 0.42 per cent. On the other hand, Thodorescu[3] reported fifty cases of renal calculi in 140 autopsies, the majority in patients under 6 months of age.

Compared with incidences reported in the literature, the number of patients treated in this hospital's pediatric department is high. It is 22.6 times higher than the yearly incidence reported by Lett[2] and 125.3 times higher than the incidence reported by Joly.[3]

For this purposes of this paper the incidence of pediatric urolithiasis patients is expressed in terms of percentage of the total number of hospitalized children in the pediatric departments for the specified period of time. Such an evaluation permits comparison of the incidence in the different ethnic groups on a statistically sound basis.

The over-all incidence of urinary stone cases for the 1949-1956 period of time was 0.15 per cent of all the hospitalized children. The yearly incidence is shown in Table IV.

Age When Urolithiasis Was Diagnosed.—In considering the age incidence of urolithiasis, one must remember that stones frequently grow so slowly or are so located that they cause no symptoms and therefore may have existed for many years before being recognized. Therefore the age when urolithiasis was diagnosed is used here. This corresponds with the age of appearance of symptoms, as the patients in these series were accepted as emergency cases because of acute illnesses and diagnosis of urolithiasis was made only later, during hospitalization.

Four patients were so diagnosed during their first year of life and three between 1 and 2 years of age (infancy age group, 23 per cent). Fourteen cases (45 per cent) were in the early childhood group (2 to 6 years) and the remainder (32 per cent) were diagnosed during the late childhood years, 8 to 13 years of age.

In other series reported in the literature various distributions of cases have been observed. In forty-one of the seventy-one cases (58 per cent) reported by Smith[6] the disease was recognized before the age of 5 years; in eight of these (11 per cent) diagnosis was made before the end of the first year, and in twenty-five (35 per cent), by the age of 3 years. Thomas and Tanner[5] collected 203 cases of urolithiasis with the following age distribution: forty patients were under the age of five years (20 per cent), sixty between 5 and 10 years (33 per cent), and fifty-eight (32 per cent) between 10 and 15 years. No age was stated in forty-five cases. Campbell[7] found in seventy-four cases that thirty-six (49 per cent) were in infants under 1 year of age, fifteen (20 per cent) were in children under 2 years of age, eight (9 per cent) in those under five years of age, and the balance (21 per cent) below the age of 15 years.

Sex.—The number of girls in this series—about one-third of all the patients—is rather high. Among the seventy-one cases reported by Smith[6] there were three times as many males as females. Of the 203 cases reported by Thomas and Tanner[5] 155 were males. Beer and Hyman[3] found only 149 females in 3,836 cases. The lower incidence of urinary stones in females is generally attributed to their shorter patulous urethra, through which most small stones readily pass. The higher incidence in our series can be a reflection of the early age at which most female patients were diagnosed (Table II).

Ethnic Groups.—The thirty-one patients reported here came from four ethnic groups: the Ashkenazic Jews

TABLE IV. INCIDENCE OF UROLITHIASIS AMONG CHILDREN HOSPITALIZED FOR ALL DISEASES

YEAR OF HOSPITALIZATION	TOTAL NUMBER OF PATIENTS	NUMBER OF UROLITHIASIS CASES	PER CENT OF TOTAL NUMBER OF PATIENTS
1949	1,134	1	0.09
1950	2,169	1	0.05
1951	2,458	1	0.04
1952	2,703	3	0.11
1953	2,547	5	0.19
1954	3,071	8	0.26
1955	2,967	6	0.20
1956	3,203	6	0.18
Total	20,252	31	

group, the Yemenite Jews group, the Eastern Jewry group, and the Israeli Arab minority group. No patients came from the Sepharadic ethnic group. Therefore in considering the incidence of urolithiasis in the different groups, the patients belonging to this community have been excluded from this comparative study.

The Ashkenazic group of Jews in Israel is made up of German Jews who left their motherland in the early thirties; the pioneers that emigrated to Israel from Poland, Russia, and the Baltic countries in the first twenty years of this century; and the remnants of the Jewish communities of Central and Eastern Europe who escaped death in the concentration camps of Nazi Germany. These remnants were concentrated in camps for displaced persons after the end of the Second World War. Many of them immigrated illegally before Israel was established as a State. The rest came with the mass immigration wave in the 1949 to 1951 period and underwent many hardships. However, most of these immigrants were absorbed in the economic life of the country and in a rather short period of time returned to better standards of life.

The Yemenite Jews have been a minority group in Yemen for centuries. Here they lived in closed Jewish quarters secluded from the local Arab population. The overwhelming majority of them were very poor. In order to reach Israel they crossed the Yemenite kingdom to Aden by foot, subsisting on food found on their way. In Israel the transition from their primitive life has been hard and only partially successful. They remain in this country in the poor social strata.

The Eastern Jews have not preserved their ethnic integrity, mixing instead with the local Arab population. Their community life and habits were those of the Arab population in their country of origin. In Israel the majority live in transit camps, new agricultural settlements, and the slum quarters of the big cities. They are, however, better off than in their countries of origin.

The structure of the Arab community in Israel has been severely disturbed by the War of Liberation (1948) which accompanied the establishment of Israel as a State. The well-to-do Arabs left during the great Arab evacuation of the spring of 1948, while the poorer Arabs remained in Israel. This community has clung to its ancient social, dietary, and cultural habits.

The ethnic origin of the patients in this hospital has been noted only since the beginning of 1953. Therefore the incidence of urolithiasis among the patients belonging to the different ethnic groups can be calculated only on the basis of those accepted since January of 1953. The total number of patients and the number of urolithiasis cases for these four years are shown in Table V. The incidence of urolithiasis among the Ashkenazic children treated during these years was 0.05 per cent; among children of the Eastern Jewry group, 0.19 per cent; among the Yemenite Jews' children it was 0.66 per cent; and for Arab children 0.84 per cent.

A comparison of incidences between groups shows two basic facts: (a) there is no relation between the number of patients with urolithiasis and the number of hospitalized patients belonging to the different ethnic groups;

TABLE V. INCIDENCE OF UROLITHIASIS AMONG PATIENTS HOSPITALIZED FOR VARIOUS ILLNESSES, BY ETHNIC ORIGIN

ETHNIC GROUP	TOTAL NUMBER OF PATIENTS AND NUMBER OF UROLITHIASIS CASES (THE LATTER IN PARENTHESES)				
	1953	1954	1955	1956	TOTAL
Ashkenazic Jews	919 (1)	950 (0)	889 (0)	967 (1)	3,725 (2)
Eastern Jews	964 (1)	917 (4)	1,011 (3)	1,246 (0)	4,138 (8)
Yemenite Jews	210 (2)	182 (1)	161 (0)	204 (2)	757 (5)
Arabs	158 (1)	254 (3)	404 (3)	367 (3)	1,183 (10)
Total	2,251 (5)	2,303 (8)	2,465 (6)	2,784 (6)	9,803 (25)

that is, the number of urinary stone patients is not dependent on the number of patients treated for all diseases; and (b) whereas the incidence of urinary stones is different for each ethnic group, it is relatively low among Ashkenazic children and high for the other three groups. A comparison between the Ashkenazic group children coming from European-born families and all the three other groups together, originating in Africa and Asia, shows that the incidence among the latter is about 7.5 times higher (0.38 per cent) than the incidence among the former (0.05 per cent).

DISCUSSION

Numerous factors have been suggested to explain urinary calculogenesis. Prominent among the many theories are the colloid-crystalloid imbalance theory, the vitamin A deficiency theory, the endocrine disturbance theory, and theories based on heredity, racial, and climatic influences. It is universally agreed that multiple factors are required for the formation of a urinary stone, but, in spite of much experimental and clinical evidence, neither a single one nor a group of the factors mentioned above has been definitely proved calculogenetic. The majority of urologists at present regard urinary calculosis not as a disease entity per se, but rather as a symptom of certain abnormal states within the body.[7] When the proper conditions exist, one or more of the calculogenetic factors can cause the formation of a stone.

In this series a significant majority of the children with urolithiasis belong to the non-European section of the population, namely, the Eastern Jews, the Yemenite Jews, and the Arab minority group, whereas relatively few came from Ashkenazic families. It is the purpose of this discussion to consider the possible abnormal conditions within the body which could have caused such a marked difference in these incidences.

It is the view of most modern urologists that calculogenetic factors can cause urolithiasis in patients debilitated by poor nutrition. Geographic studies have shown urinary stones to be rare among populations in dairy-farming countries, and to be prevalent in people living on a monotonous diet, particularly where cereals form the staple food.[7, 8] Thomson[4] reported that calculi were thirty-two times more frequent among charity patients in China than among the children of the well-to-do. With the improvement of infant and child nutrition, stones have become rare in children in the United States and England (Joly, cited by Brenner[3]). Furthermore it has been observed that when inhabitants of countries where calculogenesis is rife are settled elsewhere,

they preserve the tendency toward urolithiasis only so long as they preserve their tribal and ancestral food and community habits. When food and feeding habits are improved, the incidence of urinary stones steadily diminishes.[7] On the other hand, some authors still consider that there is an inherited disposition to urolithiasis.[9]

In the present series one is impressed by the scarcity of cases among the children of one ethnic group, and their abundance among the other three. If the influence of a factor as poorly defined as inherited disposition can be considered responsible for this difference in incidences one would expect to find this higher frequency among non-European Israelis to be present in later life as well. This is not so. There is a higher frequency of urinary stones among adults of the Ashkenazic group than among Yemenite and Eastern Jews.[10]

The three non-European ethnic groups in Israel do have in common a poorer nutritional state of their infants and children, whose diets are particularly poor in proteins of animal origin, vitamins, and fats and are rather rich in carbohydrates.[11] These essentials are absent in adequate quantities from the very beginning of their lives because of the insufficient milk of the lactating mothers, who subsist on an inadequate diet. Their condition is further aggravated by the persistence of non-European mothers in breast feeding for periods long past the first year of life. In these children the persistent and prolonged poor nutrition could have caused the abnormal conditions within the body in which the various calculogenetic factors can cause the formation of a stone.

In a certain number of children suffering from urolithiasis and belonging to the non-European ethnic groups, the nutritional history appeared to have been satisfactory. In these cases all the possible metabolic disturbances, such as cystinuria, and urogenital abnormalities should be excluded, before considering the possibility of an inherited disposition. In our cases such an investigation has not been performed.

It is our view that the greater frequency of lithiasis among the Yemenite Jewry group, the Eastern Jewry group, and the Arab children is related principally to the deficient food diet.

As the mode of life and the social and food habits of the different Jewish communities in Israel improve it should be possible to test this hypothesis in a long-range study.

SUMMARY

Thirty-one patients with urolithiasis were admitted to the pediatric departments of the Rambam Government Hospital in Haifa between 1949 and the end of 1956. The great majority among these children came from the Yemenite and Eastern Jewry ethnic groups and the Israeli Arab minority. There were only four cases coming from Jewish families originating in Europe, the Ashkenazic ethnic group. We suggest that this inequality in the distribution of cases among the different ethnic groups is due to the differences of nutritional and communal ways of life predominately, and not to ethnic inherent qualities.

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Cure for the Flux

For my Part I must confess, that if Astringents are first to be used in the Cure of this Flux, I should rather chuse to adopt my good old Master's humorous Prescription to one of the good Ladies of the Country, that had often tried his Patience with her frivolous Requests—among the rest she desired to know how she should cure her Child of the Flux? His Direction was to turn him upon his Head and stick a Cob in his A-se.

CONNECTICUT GAZETTE, September 20, 1776.

PROCTALGIA FUGAX INFANTUM

Painful Defecation in Allergic Infants

Carroll M. Pounders, M.D.
Oklahoma City, Okla.

MATT[1] recently pointed out that Thaysen,[2] several years ago, coined the term proctalgia fugax which refers to a syndrome in adults represented by a transitory pain in the rectum. It was suggested that this affliction was more common than the scanty literature about it would indicate. Among the numerous causes suggested was allergy, or so called "migraine of the rectum." It was pointed out that most victims of this syndrome also suffer from varying degrees of psychoneurotic anxiety and tension states. It is said to appear most frequently in women and seldom if ever in children.

The condition about to be described is seen sufficiently often to merit attention as a distinct clinical entity. It occurs during the first six months of life and sometimes lasts into the second year or longer. Major allergic disturbances practically always exist in one or both parents or in one or more of the siblings. The condition may be accompanied by other signs of food sensitivity, such as vomiting, colic, or frequent, loose, bowel movements. More characteristically, it occurs as the only manifestation of food sensitivity when the others appear to have either been prevented or controlled by dietary measures.

Address: 1220 N. Walker Ave.

The symptoms occur only preceding, during, and following the act of defecation. With initiation of the effort, the baby begins to cry out as if in agonizing pain. The face becomes flushed, the body is stiffened, and there is hyperextension of the hips and lower extremities. When it occurs in slightly older children, they may assume kneeling or squatting positions and try to hold back the bowel movement. They may require doses of mineral oil or laxatives sufficient to cause involuntary evacuations. The mother may say the child is suffering from constipation but upon being questioned she is likely to say the stools are not of the hard, constipated type. In fact they may be rather soft or loose. Doctors have often attributed the symptoms to anal fissures, but, in the typical case, none is found. Also, a tight anal sphincter is often looked for but not found. The examining finger finds little that is remarkable unless it be a rather loose and redundant condition of the rectum.

Many of these cases are seen by the proctologists and they have commented upon it more than have the pediatricians or general practitioners. Murdoch[3] has given an accurate description of it and at the same time has explained the mechanics of what takes place. He noted that, on proctoscopic

examination, there was more than the usual protrusion of the rectosigmoid into the proctoscope and into the upper rectum. Varying degrees of rectosigmoid prolapse or procidentia were present.

The following is a typical case history. J. H., a female, was born on Oct. 23, 1956, at full term. The delivery was normal. At birth she weighed 5 pounds 15 ounces and had no troublesome neonatal condition. Her mother has hay fever and her two siblings had considerable feeding difficulties during their first few months of life. They both have manifestations of gastrointestinal and respiratory allergy. In view of the strong allergic background, all forms of cow's milk were avoided and a soybean substitute was used. There was some spitting-up but no colic. At about 2 months of age, the baby began to cry out and strain with each bowel movement although the stool was soft. She is now 7 months of age and the condition is still troublesome. Her face flushes when the process starts; she straightens out the back and lower extremities and gives indication of being in great pain. She has from one to three movements daily. On at least one occasion there was a slight amount of blood with the stool. The discomfort subsides shortly following the movements and she is comfortable between times. Dr. Raymond L. Murdoch reports that proctoscopic examination up to 10 cm. is practically negative as is digital examination.

No doubt there are anatomical conditions peculiar to the age, such as the relatively greater degree of redundancy of this portion of the bowel, that make it easy for the condition to occur, but its correlation with other allergic conditions is too constant to be ignored. I can recall no case where an unmistakable allergic background was lacking. An imbalance of the autonomic nerve supply to various hollow viscera is a common allergic manifestation. A classical example is bronchial spasm occurring in asthma. This imbalance is notoriously patchy and segmental as it occurs along the alimentary tract. If the upper region is affected, pyloric spasm and vomiting occur. If the ileum is involved, there is colic with diarrhea or constipation, depending upon whether the longitudinal or circular muscle fibers are predominantly overactive. In the condition under discussion, the rectosigmoid or anorectal region is involved. Due to abnormal nervous stimuli there is segmental spasm and possibly temporary intussusception. The occasional appearance of a little fresh blood with some of the bowel movements might be evidence of this.

Every effort should be made to control the condition by the usual dietary measures. For immediate relief of the attack, Murdoch suggests temporarily inverting the infant, with hips up and head down, several times and running tepid water enemas into the rectum, using the inverted position to obtain the aid of gravity in correcting a temporary intussusception if the attack is persistent. The situation is sometimes made better by giving a daily saline enema and thereby producing one good evacuation in place of several lesser movements. Like colic, the condition tends to become less troublesome and usually disappears during the second half of the first year. A few cases persist well beyond this period.

SUMMARY

A condition of transitory proctalgia occurring in connection with defecation in infants with allergic backgrounds is presented. Its probable modus operandi is discussed. The condition is self-limited in scope with a time factor similar to that of colic.

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There is, however, an important branch of education, which, according as it is wisely or unwisely directed and controlled, exerts a most powerful influence over the character, happiness, welfare, usefulness, and, to a certain extent, over the health of every human being, and which commences the moment the child is able to form even the simplest ideas; it is the education of circumstances—of examples; insensible education, as a popular writer correctly terms it; the results of which, like those of the insensible operations going on in the physical world, are often more striking and more permanent, than of such as are open and apparent. To this education everything contributes by which the child is surrounded—the example, the conversation, the manners, the opinions, the prejudices of his parents, and of those in whose society he is frequently brought, or accidentally falls—the sentiments he hears expressed while playing unnoticed in the corner of a room, the conduct of his parents and seniors towards each other, towards himself, as well as towards others. From these influences, it is not in the power of parents, even were it advisable, to withdraw entirely their children; but it is in their power to surround them with such influences, only, as are calculated to give to the mind in early life that proper moral bias, which no light temptation, in their future intercourse with the world, will be able to destroy.

D. Francis Condie: on the Diseases of Children, 1871.

CONGENITAL DEFECT IN THE MUSCULATURE OF THE STOMACH RESULTING IN SPONTANEOUS GASTRIC PERFORATION IN THE NEONATAL PERIOD

A Report of Two Cases

John L. Meyer II, M.D.*
Staten Island, N.Y.

WITHIN the past few years, spontaneous rupture of the stomach in the newborn infant has come into increasing focus in the medical literature. In a review in 1955, Vargas and associates[1] were able to find 55 cases, dating from 1825, and added eleven cases of their own, occurring at Babies Hospital, Columbia University College of Physicians and Surgeons, over a period of twelve years. Since then, several additional cases have been added[2-5] bringing the total to better than 70.

Two cases of spontaneous gastric perforation were encountered within the space of six months in the relatively small pediatric service of the United States Public Health Service Hospital at Staten Island, New York. No similar case was found in the available records of past admissions to the hospital. While reports of spontaneous rupture of the stomach indicate that it occurs with greater frequency than was formerly thought to be the case, the lesion is nevertheless so uncommon as to be a rarity.

Because of this, and because both cases involved developmental defects in the stomach musculature in association with other congenital defects, it was felt to be worthwhile to report and discuss them.

Case 1.—The mother was a 29-year-old Negro, para 0, gravida i, whose pregnancy had been uncomplicated. She was delivered on April 2, 1955, three weeks before term, after a first stage of 7 hours and 10 minutes and a second stage of 25 minutes, assisted by low forceps. Analgesic agents used were Nisentil and Trilene.

The baby, an apparently normal, 4 pound, 3 ounce male, did well until the third day of life when he became lethargic. Distention developed a short time later, and a flat plate showed a suspicion of air in the abdomen, under the diaphragm; this impression was confirmed by additional views.

An operation was performed, under local anesthesia, approximately 4½ hours after the onset of symptoms. Air and fluid escaped as the abdomen was entered. The stomach was found to have a rent, 2 cm. in length, on the anterior aspect, near the greater curvature. This was repaired after débridement of the necrotic edges of the gastric defect, and the abdomen was closed without incident.

Pathologic examination of the surgical tissue débrided from the margin of the rupture (Fig. 1) showed complete absence of the muscularis except at one edge of the specimen. Bacterial colonies and inflammatory changes were

From the Department of Pathology, U. S. Public Health Service Hospital.

*Present address: Chief, Pathology, USPHS Hospital, 414 Clarendon, Chicago 13, Ill.

present. The most remarkable feature was the presence, throughout the abnormally thin wall, of numerous, dilated, vascular channels, felt to be hemangiomatous rather than lymphatic in nature. These channels occupied the area normally occupied by the muscularis, as well as replacing much of the mucosa, which was present in small islands interspersed between the vascular spaces.

The child did well for approximately 16 hours following surgery, when breathing became labored and developed a Cheyne-Stokes pattern. His condition grew progressively worse and he died 40 hours after operation.

CASE 2.—The mother was a 21-year-old white woman, para i, gravida ii, whose previous and present pregnancy had been uncomplicated. She was delivered on Sept. 30, 1955, ten days before term, after a first stage of 12 hours and a second stage of 17 minutes, assisted by low forceps. Anesthesia consisted of Metycaine saddle block.

The baby, a male, weighed approximately 5 pounds (estimated from postmortem weight of 2,200 grams; the child was not weighed during life because of his critical condition). The infant was found to have a massive omphalocele, with rupture and evisceration of the large and small bowel

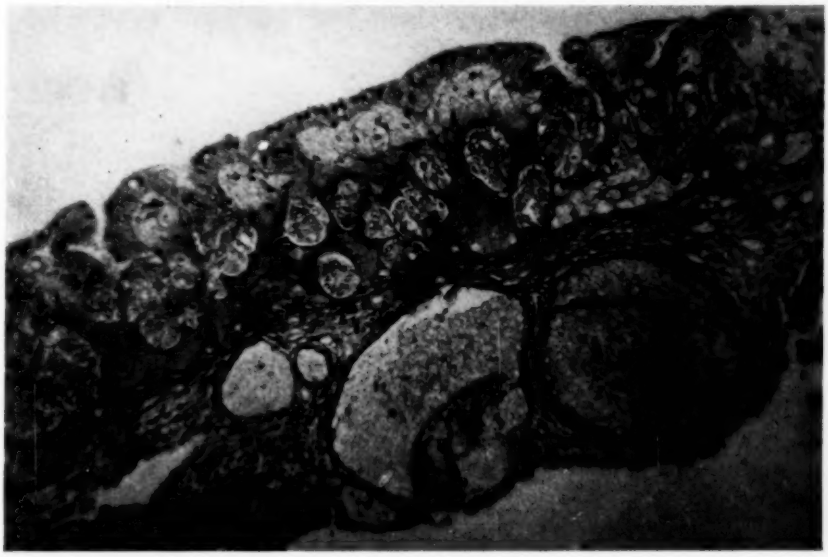

Fig. 1.—Case 1. Section taken from material débrided from necrotic edge of gastric rupture. The muscle is entirely absent, the mucosa backing directly onto the serosa. In this segment, the large number of thin-walled, vascular channels, some containing blood, are easily seen. The presence in the mucosa of these vessels isolates the epithelium into small islands. (Approx. ×150; reduced ¼.)

Necropsy revealed fibrinous peritonitis. The wound was intact, the healing process apparently unimpaired. A microscopic study of stomach and other tissues failed to reveal any additional vascular anomalies; the brain was normal. The cause of death was considered to be peritonitis resulting from the original perforation.

through a 3 cm. defect in the anterior abdominal wall. Operative repair, with exploration, was begun within one hour of delivery. The stomach was specifically examined for defects and weaknesses, because of the previous experience with ruptured stomach and the knowledge that the condition occurred at times in conjunction with

other congenital defects. No defects were apparent. Repair of the abdominal wall was difficult, because of the paucity of tissue, but was accomplished satisfactorily.

The baby did well postoperatively and began passing meconium. On the fourth day after operation, however, he became cyanotic, toxic, and listless, and later developed mild distention. The condition grew steadily worse, and the child died twelve hours after the onset of cyanosis.

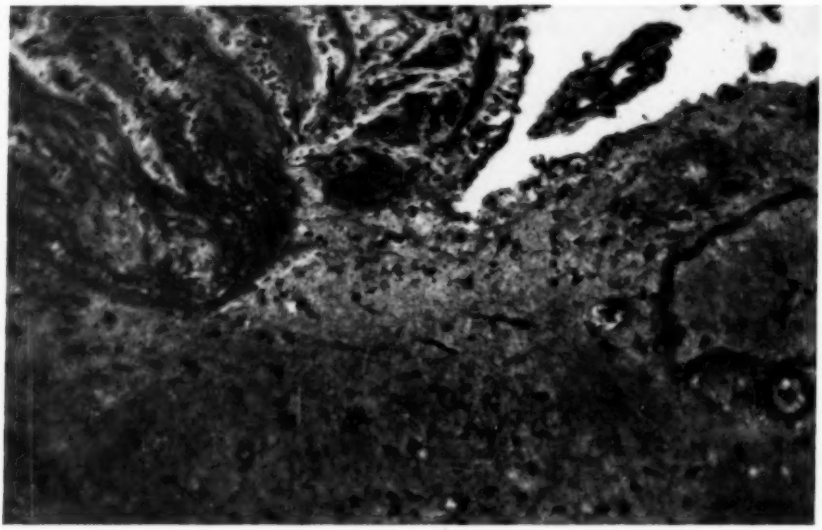

Fig. 2.—Case 2. This photomicrograph represents the rounded edge of the muscle layer (upper left) as it comes to an end near the site of rupture. The portion of the wall devoid of musculature is thickened by edema and exudate, so that the full width cannot be included in the frame of the picture at this magnification. (Approx. ×150; reduced ¼.)

Necropsy revealed free air and dark, greenish-red fluid in the abdominal cavity. The bowel was covered with plastic green exudate. The stomach had a 1.5 cm. ragged rent along the greater curvature. The abdominal wound was closed and in good condition. There was no significant brain pathology.

A microscopic examination of the gastric wall at the site of rupture revealed blunt termination of the muscularis, which was absent from the marginal tissues (Fig. 2). There was no evidence of tearing or necrosis of the muscle layer itself. This was considered to represent the edge of a congenital defect in the musculature of the stomach. Death was ascribed to peritonitis resulting from rupture of the defect.

DISCUSSION

The first comprehensive and interpretive review of spontaneous rupture of the stomach in the newborn infant was that of Herbut[6] although a smaller review had appeared earlier.[7] Herbut was able to find only fifteen cases in the literature and added one of his own, with the first account of congenital defect in the stomach musculature as an etiologic factor. He expressed the idea, since expressed by others, that muscular defects might well have accounted for or have been a factor in earlier cases and remained unrecognized because of the then prevailing concept that gastric ruptures

in infancy, like those of the duodenum, were due to ulcers. Herbut, whose case had multiple defects in the stomach wall, felt that these defects resulted from failure of the anlage of the circular layers to fuse properly.

Other etiologic factors for gastric rupture have been described and some have been proved fairly conclusively to exist. Ulceration has been shown to have been the cause[1, 7, 10] and generalized septicemia has been incriminated as well.[1] More recently, Vargas showed conclusively that polyethylene tubing can be responsible for perforation, and the presence of atresia of the intestinal tract beyond the stomach has been the apparent cause in some cases. It is not unlikely, furthermore, that some of these factors have at times been associated with muscular defects in producing gastric perforation.[3]

Abdominal trauma has been considered as a possible antecedent, but as Vargas states, it is not likely that an empty and relaxed viscus could be ruptured by birth trauma, and trauma has not been usual in the histories of these children in any case. Another concept of rupture due to ulceration involves the often observed association of such lesions with brain hemorrhage or other intracranial pathology. Rokitansky* and, later, Cushing* advanced the idea that a humoral association existed in which stress caused the damage to the stomach. As recently as 1956, Kiesewetter[2] reviewed these concepts and elaborated on them, making no mention of other known causes of gastric rupture. Some of the cases from the past and from Kiesewetter's four case reports could fit equally well into the muscular defect category.

*As quoted by Kiesewetter.[2]

It is apparent, in any case, that the majority of spontaneous ruptures located high along the greater curvature of the stomach are due to congenital muscle defects. It has been postulated that a tear in this location is practically pathognomonic for congenital muscle defect,[11] but reports exist of cases where lesions in this location were felt to be due to other etiologies[12] and at least one case is on record where a greater curvature lesion was shown definitely to be unassociated with muscle defect.[5]

A review of the literature discloses several interesting facts about defects in the gastric musculature with spontaneous rupture of the stomach. Cases falling within this narrow category number scarcely more than a dozen. The infants are often premature and, where the sex is mentioned, predominantly male (when the specific syndrome is considered, the ratio of sexes mentioned was 13:1 male to female). Frequently, associated anomalies are observed, either contributory (diverticula, atresias,) or noncontributory (clubfoot, mongolism, etc.). Race is seldom mentioned in the reports, but it is possibly of some interest that the ratio of Negro to white infants where such information is given is 8:6, including our cases.

Successfully treated cases of spontaneous rupture are rare, and, of rupture specifically due to congenital defects in the gastric musculature, only three survivals have been reported.[11, 13, 14] The diagnosis in these depended on clinical observation, since no tissue was evidently submitted for pathologic examination, in these instances. The value of submitting shreds of material débrided from the edge of the rupture was shown in our

first case, from which not only the muscular defect but the additional abnormalities in development were demonstrable while the infant still survived. And, indeed, this tissue provided the only evidence, including post-mortem examination, of the exact nature of the stomach defect.

The presence of telangiectatic vessels within the area of muscle defect constitutes a puzzling coincidence of rare anomalies. No similar case has been described, and in an exhaustive review on the subject of vascular malformations and tumors of the gastrointestinal tract in 1949, Gentry and associates[15] found no cases of intramural telangiectasia and, in newborn infants, no telangiectasis of any kind. Since such lesions are known to regress spontaneously, it is reasonable to assume that they occur in many locations where they are never detected. Had the lesion in our case not been in so critical a location—where it probably contributed to the weakness of the stomach wall—it might have regressed spontaneously without being suspected. Whether muscle defects can occur and regress spontaneously as the circular and other layers develop must remain a matter of conjecture. A preliminary sampling of the stomachs of premature infants dying of other causes has failed to reveal any defects; and a more extensive search seems warranted in order to establish whether defects can ever be compatible with uneventful development, or can play a part in the etiology of diverticula or other gastrointestinal pathology in later life.

Our cases both presented classical clinical pictures as summarized by Vargas: the fairly sudden onset of dyspnea and lassitude, with or without regurgitation, and abdominal distention in a premature infant who has done well for a day or two. Operation was prompt in the first case, but peritonitis proved too traumatic. Awareness of the possibility of muscular weakness in the second case was of no avail in preventing a tragic outcome. It is obvious, however, that early surgery and constant awareness are the only hope for saving infants similarly affected.

SUMMARY

Two cases are presented in which spontaneous gastric perforation occurred in newborn infants as a result of congenital defects in the musculature of the stomach.

The literature is brought up to date on the subject of spontaneous gastric perforation in general and perforation due to muscle defects in particular.

The association of this syndrome with other developmental anomalies is re-emphasized.

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An Early Suggestion for "Hibernation" in Tetanus

Mr. John Hunter used to say, in his lectures, "Were he to be attacked by it, he would if possible fly to Nova-Zemble, or throw himself into an ice-box." I have no doubt of the efficacy of intense cold, in subduing the inordinate morbid actions which occur in the muscular system.

BENJAMIN RUSH, 1809.

FATAL ACUTE APPENDICITIS IN A FIFTEEN-DAY-OLD INFANT

JAMES H. SHINABERGER, FIRST LIEUTENANT, MC, USA, EDWARD J. TOMSOVIC, MAJOR, MC, USA, AND WILLIAM C. BUTZ, LIEUTENANT COLONEL, MC, USA
TACOMA, WASH.

ACUTE appendicitis occurring before the age of 1 year is uncommon, and when it occurs within the first 3 weeks of life it is a rarity. In Abel's series[1] of 1,165 patients under 12 years of age only two (0.17 per cent) were under 12 months of age. Snyder[2] reviewed the world literature up to 1951 of reported cases occurring under 2 years of age. He was able to discover thirty-four cases in patients less than 1 year of age and only ten cases occurring within the first 3 weeks of life. Since that time a few reports of this disease in the very young infant have appeared.[3, 4] In some very large reported series no cases were described in patients this young.[5-9] Potter[10] describes only two cases, the infants having died of the disease at the ages of 6 and 23 days, respectively. The youngest patient in Gross's 2,070 cases of appendicitis seen at the Children's Medical Center in Boston was 6 months of age.[11]

Because of the rarity of acute appendicitis and the diagnostic and therapeutic difficulties it presents in very young infants, the following case with pathologic confirmation is considered worthy of reporting.

From the Pediatric Service and Pathology Service, Madigan Army Hospital.

CASE REPORT

A 15-day-old white female infant was admitted to the Pediatric Service, Madigan Army Hospital, on Oct. 28, 1956. Chief complaints as given by the parents were constipation and vomiting of three to four days' duration. The parents stated that the baby had done well since birth, exhibiting only the usual degree of postprandial regurgitation and a tendency to firm, infrequent stools.

Four days prior to admission a nonerythematous swelling on the right anterior abdominal wall had been noted which had spread to the right flank. At about the same time bowel movements ceased and the infant had begun to vomit small amounts after most feedings. The baby had been seen in the Outpatient Emergency Office the night of October 27. A physical examination reportedly revealed no abnormal vital signs, no dehydration, and no evidence of distress. The withholding of fluids until vomiting was controlled was suggested. A modified formula was advised to correct the constipation. The parents were instructed to return if the infant did not improve.

The following morning the baby was given a soapsuds enema, with return of normal-appearing yellow milk stool. She had continued to vomit and had become lethargic. She was then returned to the hospital. On arrival the infant appeared critically ill and was immediately admitted to the ward.

Examination of hospital records revealed that the infant had been delivered normally at Madigan Army Hospital on October 13 after an uneventful pregnancy. Initial newborn examination, course in nursery and rooming-in, and discharge physical examination were normal. She weighed 6 pounds 12 ounces at delivery, and 6 pounds 11 ounces four days later when discharged. Family history was noncontributory.

On admission to the ward, temperature was 94.8° F. rectally, pulse was 160 per minute, weight was 8 pounds 6½ ounces. (Patient was weighed with leg board restraint.) The infant had a generalized dusky cyanosis, was very feeble, and appeared critically ill. Skin turgor was fair. Head circumference measured 13½ inches. The anterior fontanel was slightly depressed. The neck was supple. Pupils were small, round, equal, and reactive to light. The tongue and lips were dry. Respiratory movements were fair. Lungs were clear and resonant, without râles. Examination of the heart revealed no enlargement, tachycardia with embryocardiac tones. There were no murmurs. Femoral pulses were easily palpable. The entire right side of the anterior abdominal wall and flank presented a circumscribed nonerythematous, nonpitting, tense edema. A 1¼ inch oval area of slightly erythematous firm induration was found in the right flank. The abdomen was distended, tight, and tympanitic. Direct or rebound tenderness could not be elicited. Bowel sounds were absent. The rectum was dilated and empty, with poor anal sphincter tone. Immediately after rectal examination, a normal yellow milk stool was passed. The remainder of the physical examination was not remarkable.

Laboratory findings were: hematocrit 64 per cent; hemoglobin 19 grams; white blood cell count 42,000; differential cell count—neutrophils 64 per cent, lymphocytes 35 per cent, monocytes 2 per cent; plasma carbon dioxide content 18 millimols per liter. Portable chest film was interpreted as showing normal heart, lungs, and thorax. Portable upright abdominal film showed moderate amounts of gas in both large and small bowel, with no fluid levels. A soft tissue swelling along the right lateral abdominal wall extending to the thorax was noted (Fig. 1). Because of the extremely poor condition of the infant, no further studies were obtained.

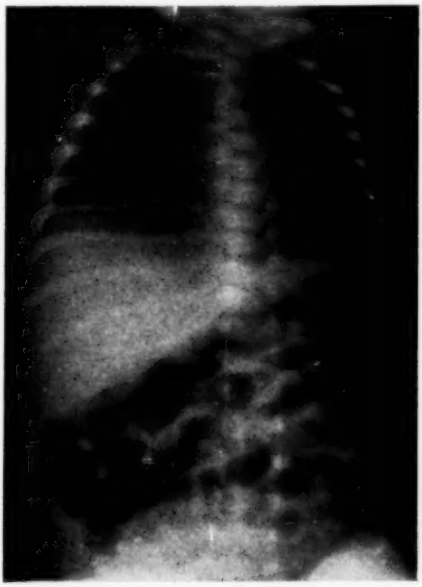

Fig. 1.—Upright abdominal scout film showing dilated loops of bowel without fluid levels. There is thickening of the right abdominal wall extending superiorly to the thorax.

A tentative diagnosis of cellulitis of the abdominal wall with probable septicemia, shock, and dehydration was established. An operable intra-abdominal condition was to be ruled out. The surgical consultant who saw the patient agreed with the working diagnosis. It was his opinion that in any event the patient was in no condition to tolerate surgery.

Intramuscular aqueous penicillin, 200,000 units, and chloramphenicol,

0.1 Gm. were given. Oxygen was administered by face mask with improvement of the cyanosis. With difficulty, a cut-down on the long saphenous vein in the left leg was performed. A generalized clonic convulsion occurred during the procedure. Intravenously administered sodium phenobarbital, 10 mg., controlled the seizure. Following installation of the venous catheter, a nasogastric tube was inserted with continuous suction and the baby was placed in an Isolette with oxygen flow at 8 liters per minute. One hundred cubic centimeters of normal saline was given rapidly intravenously, followed by a slow drip of 600 c.c. of 5 per cent dextrose in water to which were added aqueous penicillin, 2,000,000 units, and chloramphenicol, 1.0 Gm.

Initially the infant appeared to improve slightly as hydration progressed. However, eight hours after admission, the patient's condition deteriorated. Dusky cyanosis reappeared. The pulse, which had varied from 160 to 180 per minute, fell to 80 per minute and became very weak. Respiratory movements were extremely feeble and shallow. The infant appeared moribund. Adrenal cortical extract, 6.0 c.c., lanatoside C, 0.2 mg., and Coramine, 1.0 c.c., were given intravenously. Mephentermine sulfate (Wyamine), 5.0 mg., was given intramuscularly.

For a period of two hours the infant responded favorably. Pulse rose to 120 beats per minute and heart tones were of better quality. Respiratory movements remained shallow and cyanosis persisted. Rather suddenly, twelve hours after admission, respirations ceased. Intravenous Coramine was without effect and cardiac action ceased almost immediately. Heart blood, bladder urine, and approximately 1 c.c. of clear fluid aspirated by needle from the indurated area on the right flank were immediately obtained for bacteriologic studies.

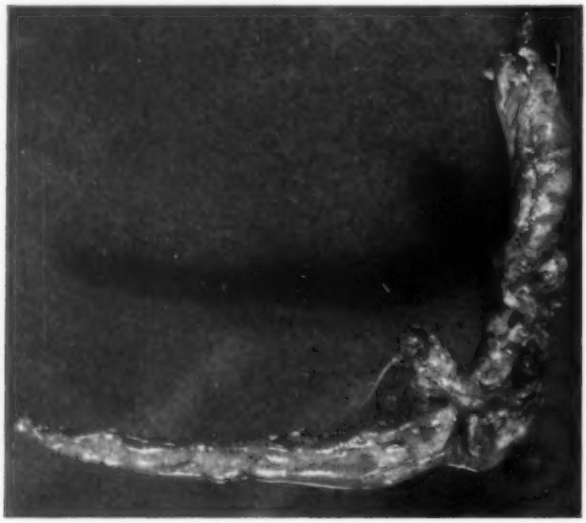

Fig. 2.—Terminal ileum, cecum, and ascending colon with the appendix bound by plastic exudate to the cecum.

Pathologic Findings.—On primary incision, the right abdominal wall revealed considerable thickening and induration. This extended laterally

into the right flank and the posterior lumbar region. The coils of small bowel were somewhat distended. A moderate amount of exudate lay over the congested serosal surfaces and there were thin fibrinous adhesions between the loops of bowel. There was no perforation. There was approximately 5 c.c. of brown purulent fluid within the pelvic cavity.

which was liberated by sharp dissection, revealed the appendix in a retrocecal position, surrounded by plastic yellow exudate. It lay in the long axis of the cecum and ascending colon, with the tip adherent to the undersurface. The mesoappendix was indurated and covered with thick exudate. (Fig. 2.) The surrounding tissues of the right para-

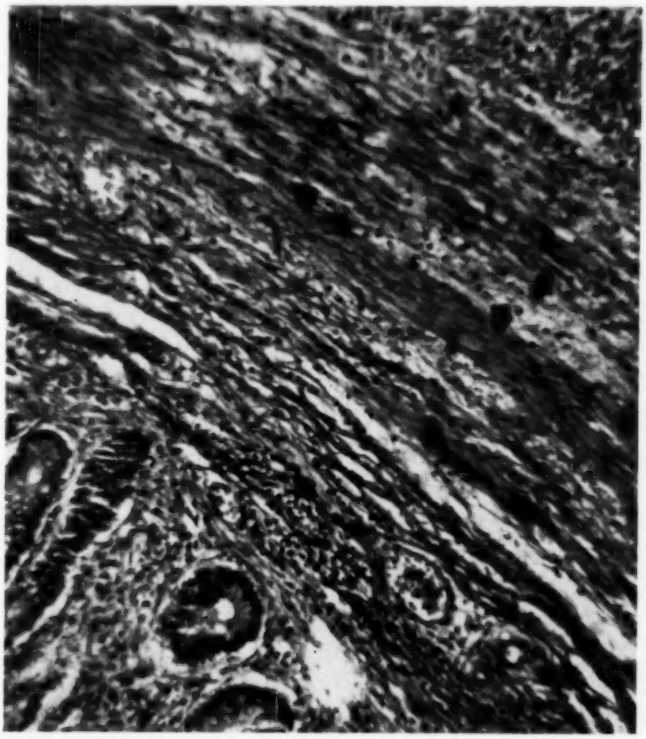

Fig. 3.—Microscopic section of the appendix showing portions of the mucosa, submucosa, and muscularis. A diffuse inflammatory reaction involves principally the submucosa.

In the right lower quadrant of the abdomen, central to the area of induration noted above, lay the dilated cecum surrounded by purulent exudate. Congestion was present in the small capillaries of the serosal surface but there was no evidence of acute inflammation of the cecum per se. The appendix was not visible from the anterior aspect. The cecum, colic gutter were also involved with intense inflammatory reaction which extended through the entire thickness of the lateral abdominal wall.

The fetal fat covering the iliopsoas muscle dorsal to the appendix was notably indurated. The remainder of the gastrointestinal tract presented no unusual features. Other parenchymal organs were unremarkable except

for a moderate amount of pulmonary edema. There was no congenital heart lesion as occurred in Potter's cases.[10]

Cultures from the heart blood drawn immediately post mortem produced no growth. Urine culture was positive for *Aerobacter aerogenes*. Cultures from the abdominal cavity in the area of the appendix taken at the autopsy table were positive for *Aerobacter aerogenes* and *Escherichia coli*. The role of these organisms as pathogenic agents responsible for the appendicitis is not established. It is likely that they were fortuitously present.

Microscopic sections revealed a diffuse suppurative appendicitis. There was infiltration of polymorphonuclear leukocytes and lymphocytes throughout the mucosa, muscularis, and subserosa of the appendix (Fig. 3). A thick layer of inflammatory exudate in which macrophages, polymorphonuclear leukocytes, and lymphocytes were identified covered the serosal surface. The appendiceal mucosa was markedly congested, and a small amount of intrastromal hemorrhage was present. Desquamated epithelial cells were present in the lumen. No obstruction of the lumen of the appendix could be demonstrated. Elsewhere within the appendix the vasculature was extremely congested. Areas of intramural hemorrhage were seen indicative of infarction and necrosis with impending perforation.

Thus, autopsy revealed a retrocecal appendix involved by an acute, diffuse suppurative appendicitis. Areas of necrosis were demonstrated microscopically within the appendiceal wall. Suppurative peritonitis was present with evidence of paralytic ileus. Death was attributed to toxemia and shock plus respiratory embarrassment from abdominal distention, all secondary to acute, suppurative appendicitis with spreading peritonitis.

DISCUSSION

Acute appendicitis is the most common cause of the acute surgical abdomen when one considers the entire pediatric age range (birth to 14 years). In infants less than 1 year of age, however, Meckel's diverticulitis, intussusception, volvulus, and malrotation are far more common causes for surgical intervention. When the rare case of appendicitis does occur in a small baby, the diagnosis is not often established ante mortem. It has been the experience of others that acute appendicitis in the very young infant is seldom recognized clinically until symptoms have been present for more than three days. Probably for this reason the incidence of perforation and peritonitis present upon hospital admission as reported by all authors is 71 per cent in the age group under 2 years.[2]

Snyder, in his review of this problem, suggests that the rarity of acute appendicitis in the very young infant is attributable to persistance of the fetal type cecum and appendix. The conical shape of the fetal appendix does not predispose to obstruction. This anatomical configuration may persist for the first few years of life. Evidence in support of Snyder's contention is the fact that acute appendicitis occurs only one seventh as often in the first year of life as in the second.[2]

The pathogenesis of the case reported here is difficult to determine. There was no luminal obstruction demonstrated within the appendix, such as ordinarily found. This occurs in the form of fecaliths, strictures, kinks, bands, diverticula, or some other obstructive phenomenon

in approximately 72 per cent of adult appendices showing acute suppuration.[12] That the appendix lay in a retrocecal position is of significance. It may safely be said that there are more complications and a greater incidence of infection in retrocecal appendices. This may result from a compromised blood supply or from obstruction due to compression by the peritoneal fold as the appendix is reflected under the cecum.

When appendicitis does occur, the likelihood of spreading peritonitis is great because of the notoriously poor defenses in a small infant. The omentum is short and thin and has almost no capacity to wall off suppuration.

Induration and inflammation of the patient's right flank are believed incident to the inflammatory process which extended from the appendix to involve the abdominal wall. The observed peritonitis undoubtedly was responsible for the paralytic ileus. Elevation of the diaphragm by distended bowel added respiratory embarrassment to the marked toxemia and shock of infection.

Failure in diagnosis in infancy is as common today as was noted by Abt[13] in 1917. Fever, constipation, abdominal pain, restlessness, and fitful sleep are frequent presenting complaints. Diarrhea is noted as an uncommon initial symptom. The position the infant assumes when undisturbed may be helpful if the thigh is flexed on the abdomen. Point tenderness is highly significant though the appendix may lie anywhere from the midline to the right flank, from the liver above to the pelvis below. Adynamic ileus manifested by distention, tympany, and diminished peristalsis on auscultation is an important finding though it may also occur in pneumonia or any other severe infection.

Early hospitalization for observation is indicated when the diagnosis of appendicitis is in question. The white blood cell count is the only important laboratory study yielding positive information on the nature and progress of the disease. Leukocytosis of 12,000 plus with 85 to 95 per cent polymorphonuclears is typical. A urinalysis and chest film complete the diagnostic workup in most cases.

Benson[14] lists some facts gleaned from the total reported experience with appendicitis in infancy.

1. The disease tends to occur most frequently in December, January, February, and March (coinciding with the season for respiratory diseases).

2. It is more common in Caucasian than in Negro infants.

3. The incidence of occurrence in males is twice that in females. (Gross's figures show only slightly more males than females.)

4. It occurs most commonly in the age group of 21 to 22 months.

5. The average duration of symptoms is definitely three days or more, and at least two thirds of the cases will have peritonitis when admitted to the hospital.

The useful limitations of this listing become apparent when it is checked against the case reported here.

It is of interest that one other case of acute appendicitis in a 3-week-old infant presented as abdominal wall cellulitis and septicemia.[3] This is obviously a late sign but may prove

useful in diagnosis, particularly if it is recognized before the advent of shock.

If the disease is diagnosed early, prompt appendectomy is obviously proper therapy and favorable mortality experience should be expected. Where diagnosis is delayed until peritonitis supervenes, the course is not so clearly evident. Expectant treatment should never be chosen as definitive since death will occur before an abscess ever forms. The infant's feeble capacity for walling off infection has been previously commented upon. On the other hand, operating upon a patient whose condition is poor because of dehydration, electrolyte imbalance, fever, or shock is an invitation to disaster.

A suitable program is to correct shock and dehydration with intravenous infusion, to employ intestinal decompression, antibiotics, and sedation. After 4 to 8 hours of preparation, when the pulse has dropped below 140 per minute and the temperature below 103° F., operation should be performed.[11]

Successful treatment hinges upon carrying the infant through appendectomy. This, in turn, demands a correct diagnosis. The knowledge that acute appendicitis may occur in the very young infant is necessary if one is to have the high index suspicion without which the diagnosis may never be made.

SUMMARY

1. A fatal case of acute appendicitis presenting as abdominal wall cellulitis in a 15-day-old infant is reported with pathological findings.

2. The rare occurrence of this disease in the first three weeks of life is emphasized and reasons for this discussed.

3. An approach to the diagnosis and treatment of acute appendicitis in the infant is presented.

Photographs by Medical Illustration Section, Madigan Army Hospital.

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APPENDICITIS IN THE NEWBORN INFANT

RICHARD H. WALKER, LIEUTENANT (MC) USNR*
MEMPHIS, TENN.

ALTHOUGH appendicitis is a common disease of childhood and young adulthood, its occurrence in infancy is unusual and, in the newborn period, quite rare. As with many diseases, the diagnosis must be thought of by the physician if it is to be established and thus the disease effectively treated.

One of the most perplexing problems which confront the physician is the enigma of correct diagnosis of disease in the newborn period of life. Most diagnosticians feel that the patient's history, in his own words, is the single most valuable factor in establishing the cause of the illness. In spite of the absence of this important factor, pediatricians have developed a very high degree of skill and accuracy in diagnosis. By using the simple methods of observation and careful physical examination, by reviewing the mother's obstetrical history, and by judiciously selecting laboratory and x-ray examinations, they are achieving increasing success in this aspect of medicine.

Improved diagnostic accuracy together with the antibiotics and our newer surgical techniques have all contributed to the steady decline in neonatal mortality. This decline, however, has shown a tendency to level off since 1950.[1] If prematurity and birth injuries are excluded as the major causes of neonatal death, there remains a small group of diverse diseases, many of which can be effectively treated.

The rarity of appendicitis in the newborn period is attested by Gross,[2] who, in reviewing over 2,000 cases of appendicitis in children seen at the Boston Children's Hospital up to 1951, states that they have not seen a single case in a patient under 6 months of age. A review of the American literature since 1950 reveals only four case reports of appendicitis in newborn infants.[3-6] There are, however, isolated reports in the foreign literature, and to date there have been approximately thirty-five case reports of appendicitis in the newborn in the world literature. This includes several associated with hernial sacs and four designated as prenatal.[7] The majority of these cases were discovered at autopsy, although in a few laparotomy was performed and at least two had a favorable outcome.[4, 5]

Two case reports are presented here for comparison with the four cases reported in the American literature since 1950. One of these infants, K. L. B., was seen at this hospital, and the other case, that of B. B. R., was contributed by Captain L. L. Haynes, Chief of

From the U.S. Naval Hospital.

The opinions expressed are those of the author and do not necessarily reflect those of the Department of the Navy or the Naval Service at large.

*Present address: Institute of Pathology, University of Tennessee, 858 Madison Avenue, Memphis, Tenn.

Surgery at the U. S. Naval Hospital, Chelsea, Massachusetts.

CASE REPORTS

CASE 1.—B. B. R., a premature Negro male, was born to an 18-year-old gravida iii, para ii mother after an uncomplicated gestation and delivery. Delivery was accomplished under saddle block analgesia. The infant at birth weighed 4 pounds, 7½ ounces, and appeared to be in fair condition.

Fig. 1.—Terminal ileum, cecum, and appendix showing anterior perforation of appendiceal tip and gangrene of the distal two-thirds. The proximal third of the appendix is retrocecal.

Physical examination of the baby showed nothing remarkable except for prematurity. The course was normal until the fifth day when, because of a poor sucking reflex, he was started on feedings by gavage. On the seventh day he became lethargic and developed retracting respirations. Examination at this time revealed a few râles in the right posterior lung field. Suction was used and the head was elevated. Later in the day he became listless and unresponsive. The Moro reflex was absent and the abdomen was said to have a "doughy feel" to palpation. Laboratory data revealed a white blood count of 4,400 per cubic millimeter, with 26 per cent polymorphonuclears, 72 per cent lymphocytes, and 2 per cent normoblasts. The hemoglobin and red blood count were normal. The spinal fluid likewise was not remarkable. A stool culture was reported later as negative for pathogens. A roentgenogram of the chest revealed normal structures. Therapy consisted of penicillin, streptomycin, and intravenous fluids. On the eighth day he vomited dark-brown mucus which was guaiac positive. Spasms of the extremities were noted and respirations were shallow and irregular. The temperature never rose above 99.2° F. He died on the eighth day, seventeen hours after the onset of symptoms.

Autopsy.—The baby weighed 1,900 grams. Slight icterus was present. Focal atelectasis was observed, but otherwise the chest revealed no abnormalities. In the abdominal cavity

there was a diffuse fibrinous peritonitis, and the distal two-thirds of the appendix was gangrenous and covered by strands of fibrin. Microscopically, the appendix showed coagulative necrosis, inflammatory cell infiltration, and thrombosis of the vessels. Cultures of the peritoneal fluid were positive for *Escherichia coli* and *Pseudomonas aeruginosa.*

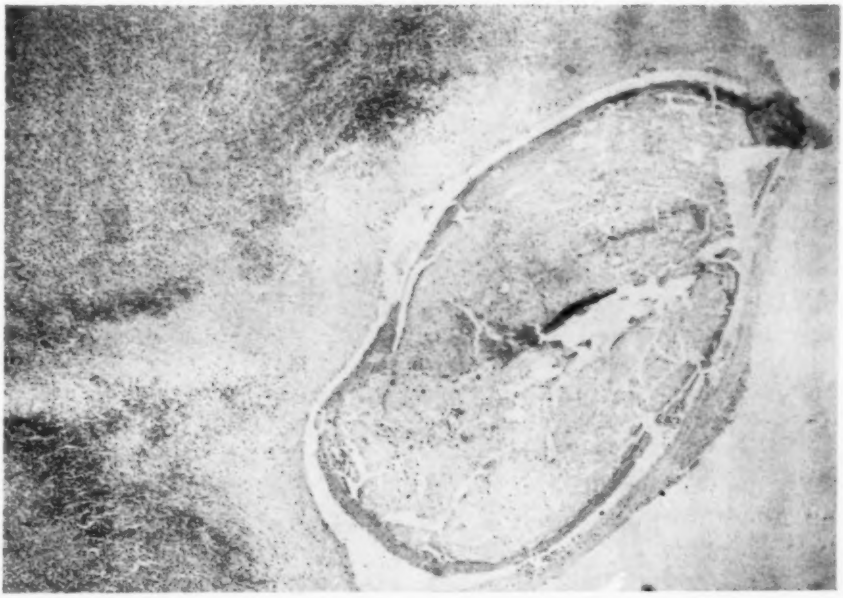

Fig. 2.—Section through appendiceal tip close to site of perforation showing fecal concretion filling the lumen and hemorrhage and necrosis of the appendiceal wall. (×60; reduced ⅙.)

CASE 2.—K. L. B., a premature white female, the first of twins, was born to a 17-year-old primigravida after thirty weeks' gestation. The pregnancy and labor were uneventful. Delivery was accomplished under saddle block analgesia. The infant presented as a single footling breech and was delivered without complications. The birth weight was 3 pounds, 7½ ounces. Physical examination of the baby was negative except for the marked immaturity and a slight cyanosis which improved promptly when she was placed in an incubator with oxygen. The course was uneventful until the tenth day of life when it was noticed there was a short period of apnea following a feeding. Suctioning resulted in slight improvement but respirations remained irregular and shallow. The abdomen was somewhat firm but not distended. Following this episode the feedings were withheld but the baby continued to have periods of apnea and cyanosis. No blood or spinal fluid cultures were obtained. The temperature was never elevated above 98.6° F. The baby died on the eleventh day, seven and one-half hours after the onset of symptoms.

Autopsy.—The infant weighed 1,425 grams and was poorly developed. Examination of the chest revealed focal atelectasis bilaterally with a fibrinous pleuritis involving the right middle and lower lobes. The peritoneum was covered by fibrinopurulent material which matted the intestinal loops and the omentum. The distal two-thirds of the appendix was gangrenous, and

TABLE I

CASE	RACE AND SEX	BIRTH WEIGHT (LB.-OZ.)	AGE AT ONSET OF SYMPTOMS (DAYS)	DURATION OF ILLNESS	AGE AT DEATH	SYMPTOMS	FEVER	W.B.C.	PATHOLOGY
Meyer[3] (1952)	F	3-9	4	5 days	9 days	Vomiting; abdominal distention	No	Not reported	Gangrenous appendix; localized peritonitis
Meigher and Lucas[4] (1952)	F	4-5 Triplet	10	24 hr.	Survived surgery	Abdominal distention; loose stools	100.8	Not reported	Acute suppurative appendicitis; no peritonitis
Riddell and Mullins[5] (1954)	WM	3-12 Twin	15	7 days	Survived surgery	Abdominal distention and firmness	No	25,400	Gangrenous appendix; no peritonitis
Baker[6] (1954)	M	7-9	4	18 hr.	5 days	Diarrhea; vomiting; abdominal distention	101	6,100	Gangrenous appendix; diffuse peritonitis
Haynes (Case 1) (1954)	CM	4-7½	7	17 hr.	8 days	Listlessness; respiratory difficulty; doughy abdomen	No	4,400	Gangrenous appendix; diffuse peritonitis
Walker (Case 2) (1956)	WF	3-7½ Twin	10	7½ hr.	11 days	Cyanosis; respiratory difficulty; firm abdomen	No	Not reported	Gangrenous appendix with perforation and diffuse peritonitis

there was a 1.5 mm. anterior perforation of the tip surrounded by fecal material and exudate (Fig. 1). A fecal concretion was present within the lumen of the middle third and on microscopic examination the distal appendiceal wall was necrotic and infiltrated by acute inflammatory cells (Fig. 2). Numerous clumps of bacteria were present within the appendiceal lumen. Gram stains revealed a mixed flora of gram-positive and gram-negative organisms with staphylococci predominating.

COMMENT

In this small series of six cases (Table I) there are three of each sex, and all but one of the babies were premature. Multiple birth was present in three instances. The age at onset of symptoms varied from 4 to 15 days and the duration of the illness varied from 7½ hours to 7 days. The most common symptoms were vomiting and abdominal distention associated with either firmness or a doughy sensation on palpation of the abdomen.

As with many other overwhelming infections in the newborn period, fever, leukocytosis, and the usual signs of infection may not appear, even in the presence of peritonitis. All appendices in this series were gangrenous except one which had suppurative inflammation. Peritonitis was present in four cases.

The infrequency of appendicitis in the newborn and infant as compared to later childhood has been attributed to[8]: (1) the fetal type or funnel-shaped appendix in the newborn; (2) the milk and soft food diet in the newborn and infant; (3) the recumbent posture of the newborn; (4) the infrequency of respiratory and intestinal infections in the newborn.

All of these theories are based on the supposition that intraluminal obstruction is the underlying factor in the pathogenesis of appendicitis. The organisms most commonly isolated from infected appendices are of the coliform group, alone and mixed with gram-positive cocci.[2]

There is a very high mortality rate associated with appendicitis in infancy. Greene[9] in 1949 reported a mortality rate of 44 per cent in patients with appendicitis under 2 years of age. All appendices except one were found to be ruptured at the time of operation. Snyder and Chaffin[8] in 1952 reported twenty-one cases of their own. They reviewed the literature on appendicitis in infancy and found that 447 cases had been reported up to that time. In 71 per cent of all reported cases perforation, peritonitis, or abscess had developed by the time the diagnosis was established. The overall mortality reported in the literature was 29 per cent, and in their series 19 per cent. The decrease in mortality was attributed to earlier diagnosis, more prompt surgical intervention, and the advent of more potent antibiotics.

The high mortality rate of appendicitis in the newborn and infant has been attributed to the following.[2, 3, 4, 6]

1. The delay in diagnosis—most important.

2. The higher incidence of perforation and peritonitis, due to: (a) the very thin-walled appendix with a meager blood supply; (b) the inelasticity of the appendiceal wall due to the large amount of lymphoid tissue present; (c) the relatively large size of the appendix as compared to the rest of the

gastrointestinal tract; (d) the small, undeveloped omentum, which does not afford a good envelope; (e) the relatively longer mesenteries for the hollow viscera, which allow more rapid spread of contamination; and (f) the relatively smaller size of the peritoneal cavity.

3. Less resistance to infections.

4. The more delicate fluid balance in infancy, due to the greater fluid requirements and the frequency of dehydration and acidosis.

SUMMARY

Although appendicitis is rare in the newborn infant, it must be considered in the differential diagnosis of acute abdominal conditions in this age group. The most common symptoms include abdominal distention and vomiting, associated with either firmness or a doughy sensation on palpation of the abdomen. Fever and leukocytosis are not constant findings in these cases. Only with a high index of suspicion and the close cooperation of the pediatrician and the surgeon can these acute abdominal emergencies be diagnosed and successfully managed.

I wish to thank Dr. James Etteldorf for his helpful suggestions in the preparation of this paper.

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UNUSUAL AURICULAR FLUTTER IN NEWBORN INFANT

Report of a Case and Review of the Literature

L. E. Siderides, M.D., N. A. Antonius, M.D., and A. Richlan, M.D.
Newark, N. J.

PAROXYSMAL tachycardias in infancy are very rare. They produce a distinctive type of clinical entity from the tachycardia occurring in older children and adults and can be readily recognized if kept in mind.

Some sixteen cases of congenital supraventricular tachycardias well authenticated are reported in the literature. Of these, nine were flutters,[3, 9, 20, 27, 37, 39, 48, 49, 56] three fibrillations,[16, 55, 57] and the rest classified as supraventricular tachycardia.[2, 8, 45, 50, 54] Those cases were suspected during the fetal period and had been detected as irregular or very rapid rates from six months to three hours before birth.

A good number of the cases of auricular flutter and paroxysmal tachycardias reported later in infancy and childhood may also be congenital.[1, 7, 23, 32, 34, 42, 44, 52, 61]

Generally speaking, the actual incidence of congenital supraventricular tachycardias in early infancy is greater than the reported number of cases, as some of them pass unnoticed and revert to normal without being detected, while the rest are diagnosed later in infancy, such as the cases of De Bruin,[12] Doxiades,[11] and Manheimer.[32]

The subject has been extensively dealt with in articles by Prince and associates,[44] Hoyer and Lyons,[24] Anderson and Adams,[3] Nadas and coworkers,[38] Hubbard[26] and others.[2, 8, 17, 21, 32, 36, 40, 53, 62] The majority of the cases of paroxysmal tachycardias in infancy are transitory and no developmental or other causes can be attributed to them. However, a number of fetal arrhythmias in infancy associated with fibroelastosis, hamartomas, and rhabdomyomas have been reported.

It seems to be beyond doubt that in the above-mentioned cases there was some blocking in the production, or defect in the propagation, of the impulses from the primary pacemaker and hence an arrhythmia arising from heterogenetic foci in the auricles.

This paper contains a report of auricular flutter in a newborn infant. The arrhythmia was detected during the sixth month of fetal life as a fast and irregular rate. The presence of flutter and later the persisting fibrillation and the fatal outcome for the patient led us toward detailed investigation of the histologic structures of the heart, which revealed the presence of fibroelastosis and ectopic skeletal muscle fibers involving the sinoauricular node. The above findings were most probably etiologically related to the congenital arrhythmia of our case.

This case of flutter is unique because of its association with the previously mentioned anatomic defects. In reviewing the literature we were unable

From the Departments of Cardiology and Pediatrics, St. Michael's Hospital.

to find another case of flutter with similar combination of structural abnormalities.

CASE REPORT

D. W., a male infant born May 5, 1955, of a 22-year-old, healthy, white primigravida, was the product of a noncomplicated pregnancy, and full-term delivery with the use of low forceps. During the sixth month of gestation a fetal cardiac irregularity, consisting of a rapid irregular rate, was noted by the attending obstetrician. Delivery was effected by saddle block anesthesia.

Examination at birth revealed an eight-pound male infant, with generalized cyanosis. Cry and respirations were not unusual. The lungs were clear. An initial observer heard a grade 2 systolic precordial murmur. The heart rate was 115 per minute and regular.

An electrocardiogram taken shortly after birth revealed a 4:1 pure auricular flutter with an auricular rate of 460 per minute and ventricular rate of 115 per minute. During the recording, the rate reverted to auricular flutter fibrillation with occasional aberrant ventricular responses and remained as such thereafter. (Fig. 1.)

X-ray of the chest taken the same day revealed marked cardiac enlargement of a diffuse type. The laboratory findings were within normal limits. The patient was placed in an oxygen tent, digitalized with Cedilanid intramuscularly, 0.03 mg. per kilogram, and maintained on Digilanid, 4 Gtt. daily.

The following day, the cyanosis gradually subsided and a murmur could no longer be heard. He continued to fibrillate and had a ventricular rate of 150 to 180 per minute.

He was discharged on May 12, 1955, on a maintenance dose of 4 Gtt. daily of oral Digilanid and there were no congestive phenomena on discharge. Periodic examination by the private physician revealed normal growth and development despite the persistence of fibrillation.

On Aug. 11, 1955, he was readmitted because of persistent restlessness and pallor. There were no changes in the physical examination except for diffuse cardiac enlargement and liver enlargement of 3.5 cm. below the right costal margin. An additional dose of 0.175 mg. Cedilanid was administered on the following day without any effect on the ventricular rate, which remained 150 to 180 per minute.

On the morning of August 15 he was examined and appeared cheerful and not in any acute distress. He died suddenly at noon the same day.

Post-Mortem Examination.—Examination revealed a moderately developed 3-month-old white male baby with myxedematous appearance, mostly in the neck. There was no evidence of lymphadenopathy, but a remarkable hypertrophic, edematous thymus covered with punctate hemorrhages throughout was present. It filled the whole supermediastinal area and weighed 50 grams. The heart was normal for the age of the baby. No developmental defects were apparent on gross examination. Examination of the coronary arteries revealed them to be of normal origin, position, and distribution. The foramen ovale was closed.

Lungs were normal. Liver was enlarged 2½ fingerbreadths below the right costal margin and its section revealed fatty changes throughout the organ. Adrenal glands were thin in section and there was atrophy of the medulla. Kidneys revealed fetal lobulation. There was marked hypertrophy of Peyer's patches and enlargement of the mesenteric lymph nodes. Unfortunately no permission to examine the brain was obtained.

Microscopic Examination.—Examination showed considerable cortical hyperplasia of the thymus gland with small number of reticular phagocytes and moderate narrowing of the medulla with mostly cellular and hyaline Hassall bodies.

Sections from the heart revealed subendocardial fibroelastosis involving both ventricles and auricles (Fig. 2). Striated skeletal muscle fibers were present in the caval side of sulcus terminalis. Those cells were huge compared with the normal syncytial cardiac muscle, with no capability of branching. Intercalated discs were absent; their nuclei were disposed at the periphery and they possessed perimuscular interstitial membrane. The above features strongly suggested the presence of skeletal muscle. Adjacent to

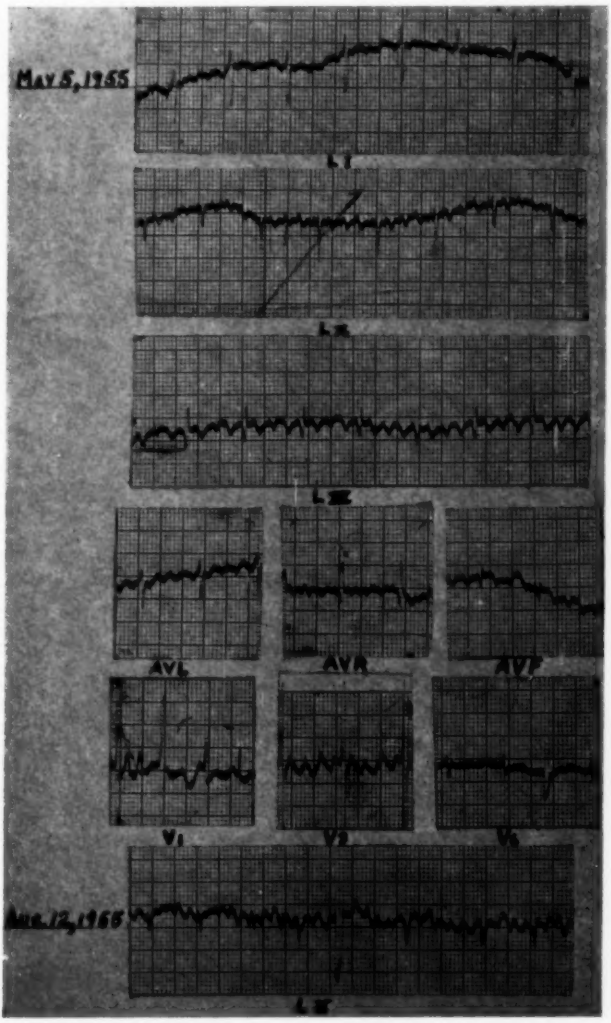

Fig. 1.—May 5, 1955—auricular flutter with 4:1 block L_1, L_2, L_3, aV_L, aV_R, aV_F; auricular flutter fibrillation with aberrant ventricular complexes in V_1, V_5. Aug. 12, 1955.—flutter fibrillation with aberrant ventricular responses, L_2.

this in the right atrium there was also marked chronic inflammation.

This was surrounded and interdigitated with many nerve fiber bundles tiguous with the sinoauricular node (Figs. 3 to 6).

Liver cells revealed parenchymatous swelling, fatty degeneration with pig-

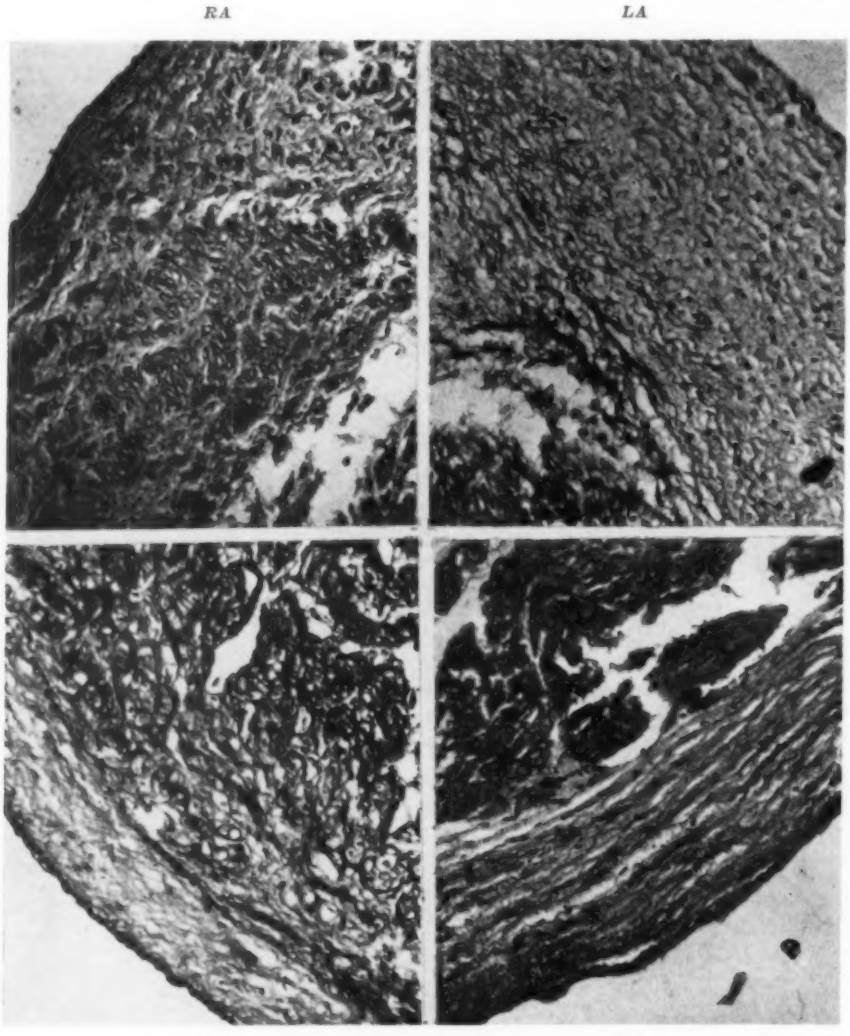

Fig. 2.—Sections through the endocardial aspect of right auricle and ventricle and left auricle and ventricle. Note the marked subendocardial fibroelastosis. (Hematoxylin-eosin stain; ×150; reduced ¼.)

which appeared to be proliferated beyond what one normally sees in this area. These inflammatory and proliferated elements surround and are continuous with the sinoauricular node (Figs. 3 to 6).

Liver cells revealed parenchymatous swelling, fatty degeneration with pigmentation, and nuclear vacuolations. There were multiple glomerular cysts in both kidneys, some of them containing serous fluid. Some focal nephronic

juvenile sclerosis and weak basophilic casts in Henle segments and remnants of fetal nephrons were also seen.

Adrenals revealed partial fetal adipose tissue and vascular congestion, multiple extracapsular corticomata, generalized atrophy, and moderate lipoid depletion with remnants of fetal cortex. Peyer's patches were hypertrophic with marked lymphoid hyperplasia.

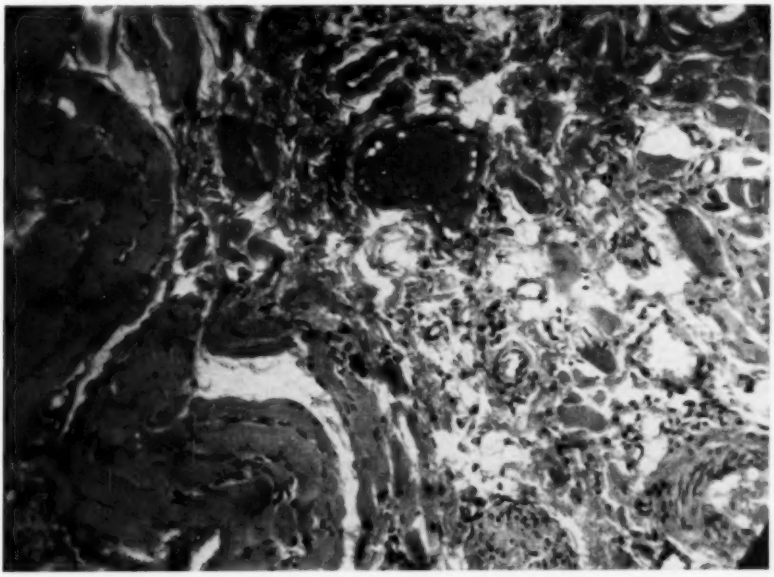

Fig. 3.—Section through the right auricle in the vicinity of the sinoauricular node. Note the contrast of the solitary skeletal muscle to the syncytial myocardial fibers. Inflammatory changes and fibrosis are also present. (Hematoxylin-eosin stain; ×100; reduced ¼.)

COMMENTS

This case of auricular flutter is unusual in many respects: In its association with fibroelastosis of both auricles and ventricles, the presence of aberrant striated muscle on the caval side of the sulcus terminalis and partly in the right atrium, and marked chronic inflammation around the sinoauricular node.

The foramen ovale was found to be closed completely at the age of 3 months. This is a common finding in the fatal cases fibroelastosis in infancy. Premature closure of the foramen ovale in fetal life and the resulting anoxemia have been considered as the cause of congenital fibroelastosis.

In eleven of the fourteen cases of congenital tachycardia, a conversion to normal sinus rhythm within one hour to one year after birth occurred either automatically or, as it happened in the majority of cases, after digitalization. Quinidine was used successfully in one case.[28] In the case of our patient, the auricular flutter lasted no more than one hour and was reverted by itself to auricular fibrillation. All attempts to convert the auricular fibrillation to normal sinus rhythm or to slow the ventricular rate were futile. Treatment with quinidine was contemplated but sudden death intervened.

The lack of response to digitalization, restlessness, anorexia, irritability, progressive failure, and death within the first months of life are the characteristic clinical findings of congenital fibroelastosis.[4, 5, 29]

The sudden death, however, could have been due to ventricular asystole following complete heart block, probably due to fatigue or involvement of the atrioventricular node.

Fig. 4.

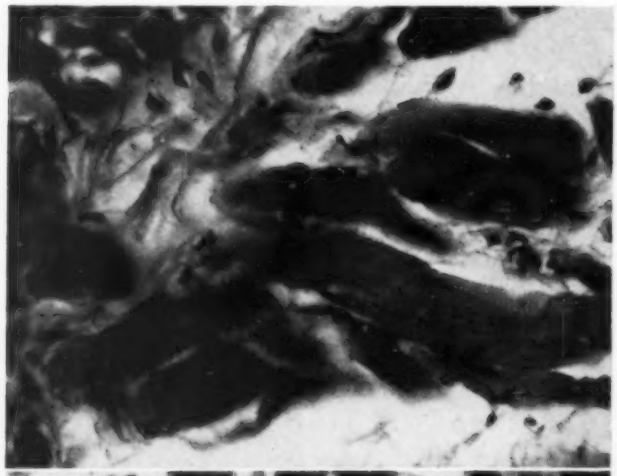

Fig. 5.

Figs. 4 and 5.—Note the typical structure of the skeletal muscle fibers with its peripherally located nuclei, absence of branching, and absence of intercalated discs. (Hematoxylin-eosin stain; ×400; reduced ¼.)

DISCUSSION

Various explanations have been offered concerning the etiologic physiopathology of congenital supraventricular tachycardias.

Inflammatory changes of either layer of the cardiac wall, as well as those involving the conduction system, have been considered as cause of this type of arrhythmia.[31, 40, 58, 59]

Dilatation of either auricle is a well-known cause of flutter and fibrillation. This again can be a result of congenital malformations, such as septal defects, anomalous pulmonary vein drainage, and Ebstein's anomaly. A variety of congenital heart disease in infancy and early childhood where auricular flutter was present have been reported. These included congenital isolated dextrocardia,[10] coaretation of the aorta,[41] Ebstein's anomaly,[56] intra-auricular septal defects,[52, 56] and transposition of the great vessels, with septal defects and patent ductus arteriosus.[51]

A number of congenital developmental anomalies associated with tachycardias have also been reported. Two cases of paroxysmal tachycardias in infants were reported by Nadas and associates.[38] Both patients died from unrelated causes, and a sinoauricular node tumor, described as hamartoma, was found in the right auricle.

Recently Appley and co-workers[4] reported a case of a 4-month-old infant with paroxysmal supraventricular tachycardia who died three hours after his admission. Marked fibroelastosis involving the left ventricle and left auricle with marked dilatation of the latter was described.

Prior to this case, congenital paroxysmal tachycardia in children with "idiopathic cardiac hypertrophy" have been described.[43, 46] Amberg and Willius[1] found marked right auricular and right ventricular dilatation in a 4-year-old child who had auricular flutter and died of congestive failure.

The tachycardias occurring in patients with fibroelastosis can be attributed either to the dilatation of one or both auricles or to the interruption of the normal pathways of the propagation and/or blockage of the sinoauricular node itself by this process.

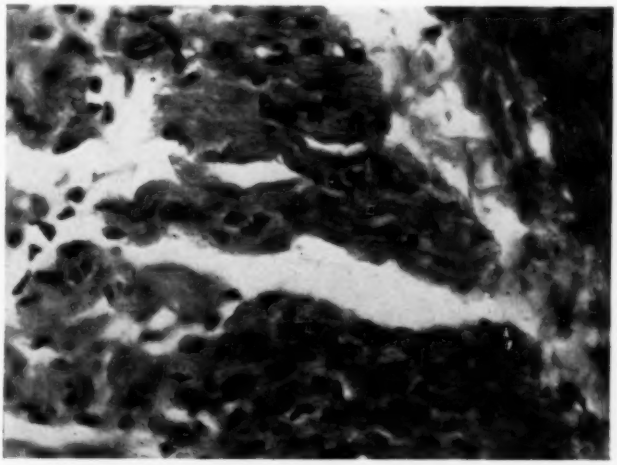

Fig. 6.—Ventricular myocardium. Normal syncytial structure. (Hematoxylin-eosin stain; ×400; reduced ¼.)

Myocardial ischemia resulting from the subendocardial fibroelastosis may play an important role in both instances.

The presence of ectopic tissue blocking the conduction system and producing flutter was well demonstrated in the case reported by Wegman and Egbert,[60] where a rhabdomyosarcoma was found to have invaded the atrioventricular node. Powers and Le Compte[43] also described a case of a newborn infant with paroxysmal tachycardia where at autopsy a small nodular rhabdomyosarcoma was present at the upper part of the intraventricular section.

Finally, the case of a newborn child with cyanotic episodes who died when 5 days old was reported by Susman and Stanley.[47] An arrhythmia consisting of frequent auricular extrasystoles clinically indistinguishable from auricular fibrillation was present.

The microscopic examination revealed several nodules of misplaced striated muscular tissue with glucogen deposition in the myocardium of all four cardiac chambers.

One can assume that in many cases of arrhythmias where congenital injury or malformation is present the latter restrains the normal stimulus formation and propagation. The fact that most of the arrhythmias in infancy occurring in cases of congenital hearts are transitory suggests that they are not always due to structural abnormalities alone. Even in cases where the arrhythmias in congenital malformations persist, it is very difficult, if not impossible, to evaluate the etiologic relations, as the histologic architecture of the conduction system in the auricles is not yet well established and the histochemical changes that occur in the auricular myocardium in such instances have not yet been determined.

Therefore, it seems very logical that, besides the anatomic defects, endogenous disposing factors, such as immaturity of the conduction system, vagal and sympathetic effects, electrolyte disturbances, as well as the influence of toxic agents and variations of the oxygen tension, should be taken under consideration whenever attempts to clarify the pathogenesis of arrhythmias are made.

SUMMARY

1. A case of congenital auricular flutter has been presented.

2. The etiologic associations of the congenital arrhythmia with the presence of fibroelastosis and ectopic striated muscle in the right auricle have been emphasized, the possible mechanisms involved in its production, and the resistance to treatment of this arrhythmia have been discussed.

We are indebted to Dr. A. Ruccia for permission to use the clinical material presented. Sincere thanks are due to Dr. M. Lev, Department of Pathology, University of Miami School of Medicine, Coral Gables, Florida, to Dr. J. E. Edwards, Department of Pathologic Anatomy, Mayo Clinic, Rochester, Minnesota, and to Dr. I. Lee, Department of Pathology, St. Michael's Hospital, Newark, New Jersey, for their kindness in reviewing and commenting on the microscopic sections.

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FAVISM

Case Report Showing Heredofamilial Tendency

Hyman C. Tolmas, M.D.
New Orleans, La.

FAVISM is caused by the ingestion of *Vicia fava* (also known as the horse bean, fava bean, broad bean) or by the inhalation of pollen from the blossom, by people having an idiosyncrasy or allergy to this substance.[1] Among the relatively few states in which the bean is grown, Louisiana harvests a large crop of fava beans annually. Only sixteen cases have been reported in the United States since 1933[2] and none were from Louisiana. This is interesting to note, since there is a large Italian population in that state and it is known that persons of Italian extraction constitute the majority of people who cultivate and eat fava beans in this country.[2]

CASE REPORT

G. R., a 2½-year-old white male of Italian descent, was admitted to the hospital on April 6, 1956, with the complaints of pallor, jaundice, and bloody urine. This child was well until one day prior to admission, when he was unable to get up because of weakness. His mother stated that he became pale and voided bloody urine. On the day the patient was brought to the hospital, he became jaundiced and continued to pass dark-colored urine. Both parents denied knowledge of his ingesting fava beans. The following day, the father related the fact that the child had had "horse beans" two days prior to admission. He was not cognizant that "horse bean" was a colloquial name of the fava bean.

The past history was noncontributory. Family history revealed that the maternal great-grandfather, born in Sicily, frequently became jaundiced on exposure to the fava plant or upon ingestion of cooked fava beans. The patient's paternal uncle also manifested symptoms of gastrointestinal disturbance (vomiting, nausea, and diarrhea) upon exposure to the pollen or upon ingestion of the fava bean. The paternal grandparents raised fava beans on a farm in Hammond, La.

Physical examination revealed a well-developed, well-nourished, acutely ill, irritable, jaundiced infant, who was extremely pale. Pulse was 140 per minute, blood pressure 100/70, temperature 101° F. The positive physical findings were limited to the heart and abdomen. There was a soft, blowing, apical systolic murmur. The liver was palpable 3 cm. below the costal margin and the spleen 4 cm. The scleras were icteric.

Laboratory findings were as follows: hemoglobin 5.4 grams, hematocrit 17 per cent, red blood count 1,910,000 per cubic millimeter, reticulocytes 8.8 per cent, white blood count 19,000 per cubic millimeter with twenty-three per cent stab cells, 37 per cent segmented cells, 34 per cent lymphocytes, 4 per cent monocytes, and 2 per cent juvenile cells. The platelet count was 636,400 per cubic millimeter. Smear tests revealed an occasional spheroeyte. The prothrombin time was 77 per cent (normal, 80 to 100 per cent). Red blood cell fragility indicated initial hemolysis at 0.40 per cent and complete hemolysis at 0.25 per cent. A

direct Coombs test was negative. The patient's blood type was O, Rh positive. The blood chemistries disclosed a urea nitrogen of 6.2 mg. per cent, a serum protein of 6.90 grams, a serum bilirubin of 0.3 mg. per cent direct and of 2.6 mg. per cent indirect. Blood culture was negative. A urinalysis showed a specific gravity of 1.019, an albumin of 2 to 3 plus, negative sugar and acetone, and microscopic findings of occasional red and white blood cells. Occult blood test on the urine was 4 plus. Urine culture was negative.

A chest x-ray presented fine mottled densities in both lung bases and in the left upper lung field, which may have represented small foci of bronchopneumonia. There was no evidence of free fluid. A flat plate of the abdomen was negative.

The patient was given an infusion of 5 per cent dextrose in distilled water, followed by 500 c.c. of whole blood. Hydrocortisone in doses of 50 mg. every six hours was administered. Ascorbic acid, 300 mg. per day, and vitamin K (Synkavite), 10 mg. in divided doses, were ordered. The patient was also put on penicillin and streptomycin to keep down secondary infection.

There was rapid improvement in the child's condition, with increased alertness on the day following admission. A repeat blood count made at this time revealed a hemoglobin of 10.1 grams, a red blood cell count of 3,700,000 per cubic millimeter, a white blood count of 12,500 per cubic millimeter, with 56 per cent segmented cells, 11 per cent monocytes, and 33 per cent lymphocytes. The urine was dark and tests showed an albumin of 4 plus, with hyaline and granular casts present on microscopic examination. On the third day, the hemoglobin was 9.5 grams. Four subsequent urinalyses were negative as were the benzidine tests for blood.

The child was discharged on April 9, 1956, and has apparently been well since.

DISCUSSION

Luisada[3] reported that 40 per cent of the cases of favism result from inhalation of pollen, and approximately 60 per cent from ingestion of the beans (based on 1,000 cases reviewed in the Italian literature). Males are affected more commonly than females. Most cases occur in childhood and adolescence, though it is known that nursing infants are not immune.[2] The incidence of favism is definitely seasonal. The clinical cases are prevalent between April and May, when the plant is flowering, and between June and July, when the mature bean is marketed and eaten.[4] This patient became ill in April.

The familial incidence is well brought out by the fact that this was the third patient with the disease in four generations of one family. Murano[5] reported an incidence of 19 per cent (twenty-five cases) of favism among 130 persons in eleven families over a period of three generations.

The mechanism by which hemolysis takes place is not known. It is believed to be a manifestation of hypersensitivity to one or more allergens in the pollen or bean.[4] Passive transfer and sensitivity to skin tests, made up of extracts from the fava bean, have been demonstrated in patients subject to this disease.[6, 7] However, there have been numerous reports of skin tests with protein extracts from the bean which were negative following the acute attack.[8-10]

The fact that this patient had a fulminating form of favism following ingestion of only several beans supports the observation that the severity of the symptoms is not dependent upon the amount of beans ingested.

Clinical manifestations have been shown to occur following inhalation of the pollen of the flowering plant.[6]

The typical signs and symptoms of icterus, anemia, fever, irritability, vomiting, weakness, systolic heart murmur, and hemoglobinuria clearly characterize the clinical picture described in favism. Symptoms occur within a few hours after inhalation of the pollen, but may be delayed two to three days after ingestion of the bean. The symptoms may vary in severity from complaints of headache, nausea, vomiting, and diarrhea (as revealed in the uncle of the patient), to the full-blown manifestations presented by our patient. A palpable liver and spleen have been reported in only one other case.[2]

The laboratory findings of normocytic anemia of considerable severity, leukocytosis, hemoglobinuria with casts and red blood cells, and normal fragility tests are typical of those described in favism.

The diagnosis of favism should be considered in a case of sudden asymptomatic jaundice in a previously healthy child of Italian extraction, who has voided bloody urine. The importance of familiarity with the other names of the fava bean was evident in this case, since neither parent knew that the terms horse bean and fava bean were synonymous. Among the more common diseases to be considered in a differential diagnosis are erythroblastic anemia, hepatitis, leukemia, hemolytic anemia,[6] and toxic hemoglobinuria due to drugs such as quinine, sulfonamides, potassium chlorate, nitrites, pyridine, and analine.[11] It was noted by Robinson[12] that many cases of "blackwater fever," in Israel, were reportedly due to malaria, with the highest incidence found to be in March and April, when the fava is flowering and the beans are eaten.

The treatment of favism entails combating shock by the use of Adrenalin and blood transfusions, administration of antibiotics, and symptomatic measures. Cortisone was used by Becker[13] in treating favism in a 2-year-old child. This patient was given hydrocortisone for a short period of time, but its value is questionable.

The mortality rate is about 8 per cent.

SUMMARY

1. A typical case of favism is reported in a 2½-year-old infant, following ingestion of the fava bean.

2. A brief review of the incidence, etiology, symptoms, diagnosis, and therapy is presented.

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IDIOPATHIC HYPOPROTEINEMIA

THOMAS J. DEGNAN, M.D.
MONTCLAIR, N. J.

IDIOPATHIC hypoproteinemia is essentially a disease of unknown etiology, characterized by a depression of serum albumin and most of the serum globulin fractions. It is a relatively rare disorder, only twenty-seven cases having been reported to date.[1] Few patients die of the disease; in the majority, especially children, "the symptoms persist, with remissions and exacerbations, from early infancy"[2]; but in some, as in our case, the process appears to be transient and reversible. Most patients do not respond to high-protein feedings, although our patient did well on such a regime. In spite of the low serum gamma globulin, the susceptibility to infection is not striking.

CASE REPORT

K. Y., a 3-year-old Negro boy, was admitted on June 19, 1956, because of a swollen abdomen of one week's duration.

The child had been in perfect health until one week prior to admission, when he developed intermittent vomiting occurring especially after breakfast and dinner. There was associated anorexia of equal duration. During these past seven days, in addition to the abdominal swelling, the mother noted a puffiness of the face and fullness of the eyes, which subsided after the child had been up and about a few hours. He had no bowel movements for two days prior to admission and no stool was returned following an enema. For the past few days the child had been urinating less. The temperature ranged between 99.0° and 99.8° F.

The past, family, and dietary history, as well as the review of systems, were all noncontributory.

The physical examination showed a well-developed boy with a temperature of 99.0° F. and a blood pressure of 112/78. He weighed 36 pounds 1 ounce. There was no periorbital or facial edema on admission. Mild pharyngeal injection was present. The heart was normal, the lungs clear, and, with the exception of edema, the abdomen was normal. No stool was felt on rectal examination. There was 1 plus edema of the upper thighs.

The hemoglobin was initially 11.5 grams, diminishing at time of discharge to 9.8 grams, probably because of excessive blood withdrawal. The white blood count on admission was 17,000 per cubic millimeter, with eosinophils 19 per cent, lymphocytes 32 per cent, polymorphonuclear leukocytes 49 per cent, and no monocytes, all returning to normal limits on discharge. Platelets were normal. Serum chlorides were 100 meq. per liter, sodium 136 meq. per liter, calcium 8.5 mg. per cent, and phosphorus 3.5 mg. per cent.

Multiple urinalyses showed normal chemical and cytologic findings; the specific gravity ranged from 1.008 to 1.0023. The BUN ranged from 6.9 to 8.0 mg. per cent. The initial urea clearance on June 20 was 37 per cent; however, output was low (19 c.c.); on July 9, it was normal.

From The Mountainside Hospital.

TABLE I. OUTSTANDING VALUES

	6/19	6/21	6/27	7/9
Total protein (Gm. %)	3.8	3.6		8.0
Albumin (Gm. %)	2.5	2.3		5.3
Globulin (Gm. %)	1.4	1.3		2.6
A/G ratio	1.7	1.8		2.0
WBC per 1,000 cu. mm.	17.7	7.5	6.1	4.6
Eosinophils, % of WBC	19.0	12.0	20.0	1.0
Cholesterol (mg. %)	190.0			
Cholesterol esters (mg. %)	76.0			
Urine albumin	0.0	0.0	0.0	0.0

TABLE II. ELECTROPHORETIC PATTERN OF SERUM PROTEINS

6/20/56	
Total Proteins	3.6 Gm. %
Albumin	2.3 Gm. %
Globulin	1.3 Gm. %
Compared with control: normal amounts of alpha 1 and beta globulins; all other protein fractions decreased, especially albumin and gamma globulin.	
10/30/56 (Addendum)—4 Months After Discharge	
Total proteins	6.8 Gm. %
Albumin	4.4 Gm. %
Globulin	2.3 Gm. %
No significant abnormality; both albumin and gamma globulin deficiencies corrected.	

A Fishberg concentration test on July 11 and a Fishberg dilution on the same day were both normal.

The patch test, trichinella skin test, and serology test were all negative. Stools for ova and parasites were negative on repeated occasions. Nose and throat cultures revealed hemolytic *Staphylococcus aureus* and *Streptococcus viridans.*

Chest film and abdominal flat plate on June 19 were negative as was the barium enema on June 25. Skeletal survey on June 28 showed no abnormal findings with the exception of fewer than normal secondary epiphyseal centers for this age. The gastrointestinal series on June 28 showed large gastric folds with possible hypertrophic gastritis. On July 3 the folds persisted.

The sedimentation rate was normal and the sickle cell preparation was negative. The total circulating eosinophil count was 2,564 per cubic millimeter. The bromsulphalein test showed 1 per cent dye remaining after 45 minutes; the cephalin flocculation and thymol turbidity tests were normal. Gastric analysis on June 21 showed no free hydrochloric acid; however, after histamine, 16° free HCl was found at the end of one hour (normal 30° to 70°). On gross examination the feces were normal with the exception of a small amount of undigested fat on one occasion; the x-ray film test for trypsin showed full activity on an undiluted specimen, with no activity on 1:5 dilution (this does not rule out deficiency); however, duodenal contents on July 4 showed the enzymes amylase, lipase, and trypsin to be present. The McClure-Aldrich test, used to measure increased salt percentage in the sweat in cases of mucoviscidosis, was negative.

Course: The outstanding findings initially were the severe hypoproteinemia and eosinophilia. The child was placed first on a regular, then on a high protein diet supplemented with multivitamins. No attempt was made to limit the salt intake. Enemas, Prostigmine, and Zymenol were given to stimulate the gastrointestinal tract. On the second day periorbital edema became manifest. During the first week, the child vomited on occasion, while his appetite and bowel movements gradually improved. The most consistent abnormal finding elicited during the course was the presence and persistence of the large gastric folds on gastrointestinal series, suggesting hypertrophic gastritis; in addition, there was hypochlorhydria. No cause for the eosinophilia could be found despite intensive search for parasitic and allergic factors. By the ninth

day the edema began to subside, becoming inapparent by the twelfth day, at which time he was without signs or symptoms clinically. On the nineteenth day, he had a normal serum protein electrophoretic pattern and eosinophil counts. He was discharged from the hospital on the twenty-first day; his weight was about 33 pounds, a loss of 3 pounds since admission. His management was entirely symptomatic and supportive.

As of Oct. 30, 1956, three and one-half months after discharge, the child appeared normal clinically and had a normal serum protein electrophoretic pattern.

DISCUSSION

Probably the earliest reference to cryptogenic hypoproteinemia with edema was made by Jungmann[3] in 1922, but the first really substantiated case was that of Myers and Taylor[4] in 1933. Their case was that of a 51-year-old alcoholic who had recurring attacks of unexplainable edema since early youth. Through their studies they concluded: "The essential abnormality seems to be in the mechanism of synthesis of plasma protein emphasized by the failure of protein feedings to influence the level of plasma proteins." A disturbance of liver function was intimated by decreased galactose and levulose tolerances.

Inadequate gastric absorption was suggested by the findings of achlorhydria in three cases by Meyer-Bisch[5]; furthermore a deficiency of some vital factor responsible for malabsorption, similar to pernicious anemia, was hinted. It should be emphasized that one of the consistent findings in the present case was the hypochlorhydria and gastritis.

Cope and Goadby[6] in 1935, having measured the nitrogen balance, concluded that there were no abnormal protein losses but rather a deficiency of production. Similarly, in 1936 Thompson and associates[7] presented the first case discovered in a child, a 2-year-old, who subsequently was found to have atrophic changes in the liver at necropsy. Having studied the effect of multiple transfusions, they felt that hepatic insufficiency rather than endogenous catabolism was responsible. The liver was also implicated by Johansen[8] in 1938 and Shick and Greenbaum[9] in 1945. Certainly the findings in our case suggested adequate liver function.

Wyngaarden and co-workers,[10] in 1952, presented a case similar to ours —a 3½-year-old boy with transitory edema, depression of albumin and gamma globulins, and eosinophilia. As in this case, they ruled out such entities as nephrosis or nephritis; however, their case suggested possible bacterial sensitization on the basis of antecedent tonsillitis and repeated attacks of upper respiratory infection. Our patient had no evidence of sensitization.

Recent data suggest deficiency in protein formation or increased catabolism. Concerning the former, Sturgeon and Brubaki,[11] in 1954, presented a case complicated by iron-deficiency anemia, the patient being cured by adding meat to the diet. Fried and Henley,[12] also in 1954, had a case suggesting allergic factors, which subsided on supportive therapy. Interestingly, Dvořak and associates,[13] in 1954, cited a case complicated by aminoaciduria,

as did Illingsworth and Finch.[14] Finally, Pierce,[15] in October, 1956, published the case of a 6-month-old child with hypoproteinemia, eosinophilia, and iron-deficiency anemia, with a deficiency of metal-transporting globulin. They speculated that the diet was deficient of iron with subsequent disruption in the hepatic enzyme function required for albumin synthesis, but that otherwise liver function was normal. Transfusion supposedly supplied the deficient factor. They ruled out increased catabolism by the normal blood NPN and BUN.

Supporting the degradation viewpoint, Albright and co-workers[16] in 1949, and Henneman and Albright[17] following the fate of intravenous labeled albumin, showed an increased rate of destruction rather than decreased synthesis. Similar studies by Bendich and Kabat,[18] and Kinsel and associates[19] corroborated this view. Finally, Schwartz and Thomsen[1] administered I^{131} albumin and measured plasma and urine radioactivity, demonstrating a three times normal turnover of albumin. They went so far as to suggest the term "hypercatabolic hypoproteinemia." They postulated hypoactivity of the adrenal cortex. Actually, eosinophilia in several cases and the lymphopenia in Franconi's[20] case might tend to support their concept.

At present, the bulk of the evidence appears to favor the degradation theory. It is interesting that the number of reported cases is mounting rapidly[21-27] and only those best suited and available have been referred to.

SUMMARY

A case is reported of a 3-year-old Negro male who had been in good health up to the onset of admission, when he presented unexplainable hypoproteinemia of all the serum proteins except alpha 1, and beta globulins. Edema and eosinophilia were present. He had no history suggesting sensitization and responded well to a high-protein diet and symptomatic, supportive therapy. The signs and symptoms, as well as the laboratory findings, were transitory in nature. An attempt was made to rule out all possible etiologic mechanisms.

Various concepts concerning possible etiology and pathogenesis have been presented. The balance of evidence seems to point to an increased catabolism of protein rather than deficient synthesis.

I wish to express my gratitude to Dr. Robert J. Waldron, for permission to use the case material. I also wish to thank Drs. John L. Work and Harry H. Stumpf, for their valuable suggestions.

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ANOMALY OF THE INFERIOR VENA CAVA

Report of Case Diagnosed in Neonatal Period

Walton M. Edwards, Lieutenant Colonel, MC, USA, and
Claude E. Bennett, Captain, MC, USA

THE following report of the absence of the distal portion of the inferior vena cava, diagnosed during the neonatal period, is presented. This is believed to be the earliest age at which such a case has been diagnosed.

CASE REPORT

A male infant was delivered spontaneously Sept. 23, 1955, after a normal prenatal course. At birth, the superficial veins of the abdomen and anterior chest wall were noted to be distended; otherwise, the infant appeared to be normal.

When the patient was 16 days old, he was referred to Letterman Army Hospital for further evaluation. Examination at that time revealed a well-developed infant in no distress, the only abnormal finding being the dilated superficial veins over the abdomen and anterior chest wall (Fig. 1). These veins were noted to fill from below upward and to increase in size when the infant cried or strained. There was neither edema nor varicosity of the lower extremities.

Laboratory studies, including hemogram, urinalysis, blood chemistries, liver function studies, nonprotein nitrogen and serum proteins, were normal. A barium swallow revealed no esophageal varices. The chest x-ray was normal. Infrared photographs (Fig. 2) revealed extensive collateral circulation over the abdomen and chest.

A venogram was performed, using 3 c.c. of 70 per cent Urokon sodium* injected through an indwelling polyethylene tube in the left saphenous vein. At one-second intervals and at 1/30 of a second exposure time, multiple exposures were made, demonstrating filling of the peripheral veins up to and including the left external iliac vein, the proximal portion of which appeared to be markedly decreased in size, and showed no communication with the common iliac vessel. The contrast media entered extensive collateral vessels through the dilated left superficial epigastric vein (Fig. 3), revealing similar findings on the right side. At no time did the inferior vena cava fill and there was no evidence of deep collateral circulation. The five-minute film demonstrated a normal excretory urogram. These films were interpreted as showing hypoplasia or atresia of the postrenal segment of the inferior vena cava and the common iliac veins.

The patient was seen in joint medical and surgical consultation, and it was felt that the collateral circulation was adequate and no surgical intervention was indicated. As the patient was asymptomatic, he was followed as an outpatient without further study or therapy. Re-evaluation at one year of age revealed a normal child, except for the dilated veins over the abdomen and anterior chest wall; there was still neither edema nor varicosity of the lower extremities.

From Pediatric Service, Letterman Army Hospital, San Francisco, Calif.

*Mallinckrodt brand of sodium acetrizoate injection.

Fig. 1.

Fig. 2.

Fig. 1.—Photograph showing distended veins in abdominal wall.

Fig. 2.—Infrared photograph demonstrating the extensive collateral circulation in the abdominal wall and the chest wall.

Fig. 3.—Photograph of x-ray taken after injection of contrast media, demonstrating the collateral vessels and the failure of the iliac vessels and inferior vena cava to fill.

DISCUSSION

A review of the literature reveals a paucity of material on developmental anomalies of the inferior vena cava. Pleasants,[1] in 1911, reviewed 328 cases of obstruction of the vena cava from all causes, and added eighteen reports of his own cases. Nine of these were considered due to "congenital obstruction" of the inferior vena cava. In only two of these cases was the diagnosis proved by autopsy. The first case was in a 54-year-old patient in whom the superficial veins of the abdomen became prominent at 52 years of age. Autopsy revealed the inferior vena cava below the renal veins to be represented by a small fibrous cord not connected with the veins of the legs. The second case was in an 18-year-old patient who died of an unrelated disease; autopsy revealed the upper part of the inferior vena cava to be a fibrous cord, the great azygous vein carrying the venous return to the heart. Four of the remaining cases were considered to be due to thrombosis. The other three patients, all males, respectively 17, 27, and 30 years of age, had enlarged superficial veins over the abdomen, first noted during infancy, and had varicose ulcers of the legs, but no edema. While no diagnostic studies were performed, findings were assumed to be due to developmental anomalies of the inferior vena cava.

Angelman and associates,[2] in 1950, reviewed the literature and reported one proved case of obstruction of the inferior vena cava due to thrombosis in a 15-month-old infant who had had diarrhea. At autopsy the thrombus was found to involve the entire inferior vena cava. They also reported a case of a child, aged 4 years 10 months, in which enlarged veins over the abdomen were noted when the child began walking at about 18 months of age. The right medial saphenous vein became dilated at 3½ years of age, and slight, pitting edema of the legs developed. An intravenous pyelogram revealed normal kidneys. While no venogram was performed, it was assumed that the inferior vena cava was involved. The finding of normal kidney function, by intravenous pyelogram and urinalysis, led to the conclusion that the lesion was below the level of the renal veins.

In the case reported here, the presence of extensive collateral circulation at birth and the radiographic appearance of the venogram suggest a developmental anomaly. While not clearly demonstrated, the defect appears to be an atresia or absence of the distal (postrenal) segment of the inferior vena cava and the common iliac veins. This is compatible with the embryology of the inferior vena cava since it has been demonstrated that the postrenal segment of the inferior vena cava is derived from the right supracardinal vein, whereas the more cephalad portion is derived from other elements of the primitive cardinal system.[3] The common iliac vessels, which did not fill during the venogram, have been shown to be derived from the postcardinal system.[3]

It is postulated that the failure of the usual development of the supracardinal veins accounts for the findings in this case. The absence of deep collateral veins which are usually demonstrable in patients with acquired obstruction, such as thrombosis,[4] and the demonstration of the peripheral veins to the point of juncture with

the veins which are derived from the posteardinal system, further suggest that, in this patient, there has been an incomplete transformation of other portions of the primitive cardinal system.

SUMMARY

A case report of an infant with apparent atresia or absence of the distal inferior vena cava and common iliac veins is presented.

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PULMONARY INTERSTITIAL EMPHYSEMA WITH AIR-BLOCK SYNDROME

EDWARD J. BERMAN, M.D.,* AND ALEXANDER J. KAHN, M.D., INDIANAPOLIS, IND.

A CASE of pulmonary interstitial emphysema with air-block syndrome is presented and pathogenesis and treatment are discussed.

CASE REPORT

A full-term female infant, birth weight 7 pounds 8 ounces, was delivered by cesarean section. A previous section had been performed on the mother due to fetal distress and the infant had been normal. The current pregnancy was uneventful. The baby breathed and cried spontaneously and was in no distress. No artificial resuscitative measures were used. The baby was pronounced in good condition at birth.

Pediatric examination when the infant was approximately 2 hours old revealed nothing unusual. The lungs were well expanded. The heart was normal and the tones were of good quality. When the infant was approximately 18 hours old she was noted to be experiencing some respiratory difficulty, which gradually became more marked. At 24 hours of age she was having definite respiratory distress. The rate was rapid. Color was moderately cyanotic, and there was marked protrusion of the sternum with respirations. Breath sounds were heard bilaterally and no râles were present, though expansion of the chest seemed limited. The heart sounds were extremely indistinct, quite different from those at the initial examination. The baby cried constantly and seemed in real distress.

*Address: 23 East Ohio Street.

X-rays taken at this time were interpreted as showing a shift of the mediastinum to the right, with atelectasis of the right upper lobe and what was interpreted as lobar emphysema or pneumatocele on the left side (Fig. 1).

The infant's condition became progressively worse. Thoracotomy was carried out the afternoon of the second day, when the patient was approximately 30 hours old. She was in severe distress, cyanotic in spite of oxygen, and the deformity in the anteroposterior diameter of the chest was quite noticeable.

Under endotracheal ether and oxygen anesthesia a left thoracotomy was performed through the fifth interspace. A marginal pneumothorax was encountered. The lung showed no evidence of a pneumatocele nor was there any difficulty with inflation or deflation of the lung. The mediastinum was remarkable for the large bubbles of air beneath the mediastinal pleura. This pleura was opened widely (mediastinotomy). Physiological saline was poured into the chest and the lung was inflated. No air leaks were observed. An endothoracic catheter was inserted and the chest was closed. Water-seal drainage was established. The child was returned to the ward in critical condition.

Postoperative x-rays taken on the following morning revealed very little change from the condition shown in the preoperative x-rays. However, the child gradually improved. Feedings by mouth were begun on the third postoperative day and the endothoracic catheter was removed on

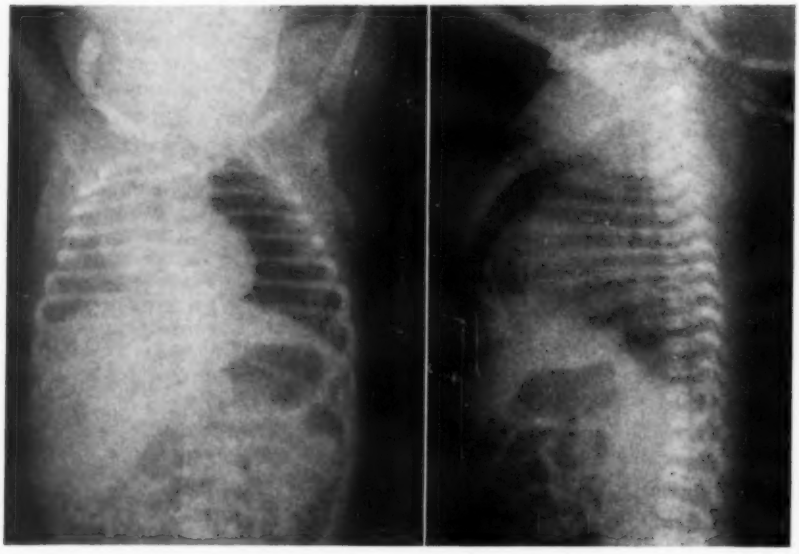

Fig. 1.—Posteroanterior view of chest showing atelectasis of right upper lobe and lateral view showing diagnostic anterior crescent of air.

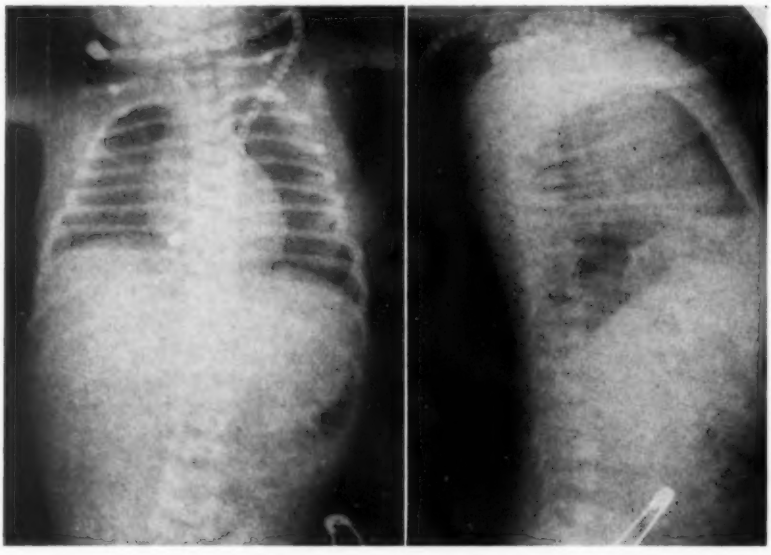

Fig. 2.—Posteroanterior and lateral views of chest taken on the fourth postoperative day, showing normal chest.

the next day. Chest x-rays taken at that time revealed a normal chest in both posteroanterior and lateral projections (Fig. 2). She was discharged on the eighth day. Follow-up x-rays one month later showed no abnormality.

DISCUSSION

Macklin and Macklin[1] in 1943 explained that pulmonic emphysema results in interstitial emphysema when air leaks through the "perivascular ring of alveoli." In this area the alveolar wall is the only structure separating lung air from the perivascular connective tissue. There are two "leakage factors": (1) The alveolar zone overdistends without a simultaneous swelling of the (adjoining) blood vessel. (2) The blood vessel shrinks without an equivalent narrowing of the alveolar envelope. Once air is "interstitial" it can easily dissect its way along the vascular sheathes into the mediastinum. Further, tension mediastinum can occur in the same way as does tension pneumothorax. Very little pressure generated through pneumomediastinum can therefore block venous return to the heart, since the mean pressures in the venae cavae, pulmonary veins, and auricles are zero or less. This, however, is but half the problem, for pulmonic interstitial emphysema per se can seriously reduce ventilatory capacity. These two factors operating alone or together constitute "air-block."

Emery[2] in 1956 reported fourteen patients who died of air-block, all infants from 4 to 49 hours old at the time of death. Two had no symptoms and were simply found dead. The others had symptoms lasting from "about one-half hour to twenty-four hours." In all cases the trachea and main bronchi were unobstructed. Air vesicles in the interstitial tissue of the lung were larger as the hilum was approached. Air was found around the hilar blood vessels. In the smaller bronchi and bronchioles plugs of mucus containing keratinized epithelium were observed. Beyond these plugs dilated alveoli were often found, and in some cases the actual point of acinar rupture into the connective tissue could be seen. The interstitial emphysema appeared to be due to mucus with amniotic debris and vernix causing obstruction in the smaller air passages. The author concludes that the "bronchi and bronchioles that are obstructed and responsible for the interstitial emphysema are too small to permit s u r g i c a l aspiration." Therefore, prevention is the best treatment and consists of removing mucus from the nose and mouth (and avoiding positive pressure resuscitation where possible). Finally, "the quick lusty yell may not be a good thing" for "a mature child can probably withstand small areas of atelectasis better than it can interstitial emphysema."

The literature contains many well-documented cases of patients surviving pneumomediastinum with air-block. Indeed, it is conceded that this condition may be far more common than is realized and that spontaneous recovery is entirely possible even after the symptoms of air-block have occurred. Certain patients, however, have appeared headed for certain death and were saved by needle aspiration of the anterior mediastinum. There are no recorded cases

of this having produced complications; indeed, there are no reported cases of this form of treatment having ever failed although several patients have required three aspirations. Yet the literature on this subject, if not clinical experience, seems limited, for there have been only two articles dealing with it in the past five years. Thus, while thoracotomy with mediastinotomy as carried out in our case might be too radical, surgical mediastinotomy might yet prove to be the safest method of treating this condition. At any rate, one might wonder how often the various conditions requiring thoracotomy in the newborn period end disastrously because of air-block secondary to positive pressure anesthesia (for example, in Bochdalek hernia requiring immediate surgery). Mediastinotomy in these patients might well become a routine part of the thoracotomy procedure.

SUMMARY

1. A case is presented of pulmonary interstitial emphysema with air-block syndrome successfully treated by mediastinotomy and water-seal drainage.

2. The pathogenesis of this condition involves the escape of lung air through alveolar rupture into the perivascular connective tissues and then into the mediastinum.

3. This condition should be suspected in the dyspneic newborn infant, particularly if the heart sounds are distant. (The diagnosis can be confirmed by radiological study of the chest.)

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Clinical Pathological Conference

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SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS 9-month-old male infant was brought to The Children's Medical Center because of poor growth rate. He was the product of a full-term uncomplicated pregnancy. His birth weight had been 6 pounds 15 ounces, and he was discharged from the nursery after seven uneventful days. He was fed a formula of pasteurized cow's milk. Solids were begun at 3 months of age. Tri-Vi-Sol had been given in a dosage of 0.6 c.c. per day since birth.

The infant was thought to be normal until the age of 6 months, at which time he developed an upper respiratory infection. He weighed 10 pounds at 3 months, and 11¾ pounds at 6 months of age. At this time the family physician noted that the infant was small for his age. No change was noted for two months, when the infant was hospitalized by another physician.

At that time the infant was found to have a bone age of 2.5 to 3 months, elevated blood urea nitrogen values ranging from 45 to 100 mg. per cent, and serum phosphorus levels between 5.8 and 8.0 mg. per cent. Urinalysis revealed a few hyaline and granular casts with a slight amount of albumin in the urine. Two intravenous pyelograms were considered normal.

A review of the significant past history revealed that intermittent vomiting had been a factor throughout life. The infant smiled at 4 months, but his motor development was slow so that he neither sat up nor crawled at 9 months of age.

There are two normal siblings of this infant.

At the time of entry to the hospital, the pulse was 180 per minute, the temperature 100.6° F., and the blood pressure 170/100 mm. Hg. The weight was 12 pounds 8 ounces. The crown-heel length was 25 cm., which is below the third percentile. The infant was well proportioned but small. He had an odd facies, with moderately prominent frontal bossing and a low nasal arch. Except for a Grade 2 systolic murmur, well localized at the left sternal border, and a right lower motor neuron facial palsy the physical examination revealed no abnormalities.

On admission the urine had pH values of 5.0 and 5.6, with specific gravities ranging from 1.008 to 1.014. No albumin, sugar, or acetone was detected in the urine. The sediment contained 6 to 8 erythrocytes and 3

to 5 leukocytes per high-power field. Hyaline and granular casts were also present. Examination of the blood revealed a hemoglobin of 8.7 grams per cent and a leukocyte count of 8,800 per cubic millimeter. The differential count gave polymorphonuclear leukocytes 39 per cent, monocytes 6 per cent, and lymphocytes 55 per cent. The platelets were judged to be adequate on examination of the smear. The serum chemistry values were as follows: nonprotein nitrogen 55 mg. per cent, sugar 126 mg. per cent, carbon chloride content 22.3, sodium 142, potassium 4.1, and chlorides 94 meq. per liter; calcium 11.5, phosphorus, 8.3, and total serum lipids 500 mg. per cent; alkaline phosphatase 4.5 Bodansky units, serum protein 5.8 mg. per cent, with 4.6 Gm. per cent albumin and 1.2 Gm. per cent globulin. The skin reaction to old tuberculin was negative. Three urine cultures grew, once each, *Staphylococcus albus*, a rare alpha streptococcus, and a rare *Colibacterium coli*. Two twelve-hour urine collections for total amino acid content gave values of 2.54 mg. and 4.62 mg.

A roentgenographic examination of the chest was negative. There was an increase in the density of the bones at the metaphyseal margins, a circular increase in density at the periphery of the tarsal bones, an increased density of the base of the skull, and also of the bones of the spine and pelvis. The intravenous pyelogram revealed poor excretion of dye by kidneys of normal size and pelvic outline.

The electrocardiogram was read as showing a P-R interval of 0.14 second (normal 0.12 at a pulse of 140), right ventricular hypertrophy, not abnormal for the patient's age, and an incomplete bundle branch block. The electroencephalogram was read as normal.

During the infant's hospital stay, numerous diagnostic tests were performed. His hypertension was not fixed, and values as low as 118/80 mm. Hg were recorded. Serum calcium levels were repeated on a number of occasions, the values reading 9.7, 11.2, 10.9, 11.3, 12.4, 13.4, and 10.9 mg. per cent. A repeat phosphorus serum determination was 6.1 mg. per cent. The hospital stay was marked by a bout of acute otitis media, which increased the severity of the facial palsy. His urinary infection did not respond to the administration of Gantrisin. Urine for an Addis count was collected and revealed a specific gravity of 1.018, erythrocytes 1.76 million, and leukocytes 154,000. On the fourteenth hospital day, biopsies of a rib, the liver, and the kidney were performed.

The patient was discharged five weeks after entry.

DISCUSSION

DR. WILLIAM B. SCHWARTZ.*—We have two major problems in this patient—renal failure and hypercalcemia. If we assume that in this child hypercalcemia was the initial disturbance, on this ground alone it would not be surprising to find some element of renal failure. We well know that hypercalcemia, regardless of its origin, very commonly leads to gross or microscopic nephrocalcinosis and renal failure. I would suspect that the hypercalcemia was causally related to the renal failure in the present case.

*Associate Professor of Medicine, Tufts University School of Medicine and Physician, New England Center Hospital.

There are, of course, other possibilities, but from the negative pyelogram we can assume that there was no significant congenital defect or obstructive uropathy to account for the observed degree of renal failure. Acute glomerulonephritis, a rare disorder in infancy, must be considered; but since there is no suggestive history, no hypertension, and no albuminuria and since the child is under a year in age, I think that as a practical matter we can disregard this diagnosis. There are findings indicative of pyelonephritis; the urine sediment was abnormal and the cultures revealed various organisms. This may be a significant factor in the disease picture, yet the kidney shadows are normal in size, there is no calyceal distortion, and it seems unlikely that pyelonephritis of the minor degree evident here would be responsible for the degree of renal failure that we see at this time. I would choose to believe that although there is an element of renal infection, the renal failure is chiefly due to the persistent hypercalcemia.

In adults with hypercalcemia we would consider many disorders which are relatively common in the older age group but are uncommon in childhood. Nevertheless, some of them do occur rarely in infancy and childhood, and for the purpose of discussion I would like to review some of these causes of hypercalcemia.

The first one is hyperparathyroidism. In this child the classical features—hypophosphatemia, elevated alkaline phosphatase, and demineralization of bone—are absent. On the other hand, bone disease and phosphatase elevation are frequently missing in hyperparathyroidism, probably due to the fact that the calcium intake in the typical American diet is so high. Furthermore, in renal failure secondary to hyperparathyroidism, serum phosphorus commonly rises to normal or elevated levels. Thus, hyperparathyroidism can occur with findings similar to those noted here. Occasionally, as the phosphorus rises, serum calcium may drop to normal, and it becomes very difficult to decide whether there has been previous hypercalcemia. Sometimes, either by gross examination or by slit-lamp examination of the limbus of the cornea at its lateral and medial aspects, one may see calcium deposition as evidenced by band keratopathy. Even though at the time of examination the serum calcium is normal, band keratopathy may occasionally persist as a residual of the previous hypercalcemia. While hyperparathyroidism cannot be excluded as a diagnosis in the present case, in view of its rarity in infants, the peculiar and entirely atypical osteosclerotic changes described in the x-rays, and the lack of other supporting evidence, I would not favor this diagnosis.

A second possibility to be considered is the so-called "milk-alkali" syndrome. This, of course, is seen chiefly in adults who have been on an ulcer regimen consisting of a high milk intake combined with free alkali. Such individuals, after a variable period of months or many years, may develop a syndrome which is much like the present one in its clinical and chemical pattern. These patients have normal or elevated serum phosphate concentration with persistent hypercalcemia and renal failure. They ordinarily have a high

carbon dioxide content in their serum, and metastatic calcification. Since none of these findings is present here and there is no history of excessive alkali intake, I think that we can dismiss such a diagnosis.

Third, multiple myeloma in the adult is a not infrequent cause of hypercalcemia. As bone destruction proceeds, the calcium is transferred to the blood at a rate so rapid that the kidneys and bowel cannot dispose of it completely and, with the resultant hypercalcemia, renal failure may result. I think that we may safely, without further ado, discard this sequence in the present patient.

A most interesting recent development has been the widespread clinical recognition of Boeck's sarcoid as a cause of hypercalcemia and renal failure. This presents a fourth diagnostic possibility. About fifteen years ago it was noted that the serum calcium is elevated in many patients with sarcoid. No comment was made at that time about associated renal damage. However, in the last three or four years there have been many reports of renal failure secondary to hypercalcemia in sarcoid, and it seems to be a not uncommon complication. We have recently seen several such cases in our clinic. This is a quite different entity from the renal failure which very occasionally occurs with sarcoid as a result of direct infiltration of the kidney. In the present patient there are no eye or parotid abnormalities, no skin lesions, and no lung lesions. I think we need not very seriously consider the diagnosis of sarcoid.

A fifth possibility is Paget's disease, which in the adult occasionally causes hypercalcemia. In the ambulatory patient with Paget's disease serum calcium is normal, but if one puts such a patient to bed, bone destruction may get ahead of bone formation and these people may develop hypercalcemia with renal failure. This diagnosis can easily be dismissed here.

The patient has a somewhat reduced plasma bicarbonate concentration. Could this be "renal tubular acidosis" or the deToni-Fanconi-Debré syndrome? Could it fall into the group of tubular nephropathies? Well, I think not. First, the persistent hypercalcemia does not ordinarily occur in these disorders. Second, we know from the protocol that the amino acid excretion is not increased and that there is no glycosuria or osteomalacia. Although it should be emphasized that the patients with "renal tubular acidosis" usually show some glomerular involvement and may, in fact, ultimately develop uremia, they do not ordinarily develop frank renal failure early in their course. In many respects, this patient does not fit the category of either "renal tubular acidosis" or the deToni-Fanconi-Debré syndrome.

A seventh possibility is hypervitaminosis D. The incidence of vitamin D poisoning reached its zenith during the period some years ago when patients were given from 100,000 to 500,000 units of vitamin D a day as therapy for rheumatoid arthritis. We still see an occasional patient on such a regimen who presents with hypercalcemia, soft-tissue calcification, nephrocalcinosis, and renal failure. We have seen one such patient within the last month who, as recently as six months ago, was taking

100,000 units of vitamin D a day. This is still a disorder of more than historical interest and is something we have to keep in mind. In reviewing the vitamin D intake in this child we have no reason to believe that the vitamin D intake was abnormal. Four to eight hundred units a day is the recommended minimal daily requirement. This child was receiving 0.6 c.c. of Tri-Vi-Sol, which contains 1,000 units of vitamin D, and if we assume that he was receiving the ordinary milk which is available in this part of the country, and which contains 400 units of vitamin D per quart, then his intake probably would have been in the range of 1,400 to 1,500 units per day. This appears, for a child of his age, to be a not uncommon intake and could hardly be considered a toxic amount by ordinary standards. However, it is noteworthy that in many ways the syndrome in this child does resemble vitamin D intoxication.

During the last year or two, the English literature has contained many reports of a syndrome which has been given the name "idiopathic hypercalcemia of infancy."[1-5] So far as I can determine from a review of the literature, no such cases have been reported, as yet, from the United States, and I wonder if the child described in this summary conceivably is the first instance of this disorder which has been seen here. There are many striking similarities between the protocol in this case and those of the infants with idiopathic hypercalcemia observed in Great Britain.

I would like to summarize, briefly, these points as they appear in the protocol and then to comment further about them.

First: The onset in the first year, with failure of normal growth and development, is classical. Second: None of the children with idiopathic hypercalcemia of infancy had been purely breast fed; in each instance the diet had contained cow's milk along with some supplementary vitamin D. This child was weaned early and was on cow's milk and supplementary vitamin D. Third: The vomiting is a typical feature. Fourth: There is the so-called "elfin" appearance, with prominence of the epicanthal folds, overhanging of the lip, and underdevelopment of the bridge of the nose and the mandible. Fifth: A systolic murmur was present in the majority of the cases and was present here. Sixth: Hypertension was found in almost every case, probably secondary to the renal failure. Initially, hypertension was found in the present case. Seventh: There were facial palsies in some 15 or 20 per cent of the cases. Eighth: Azotemia was a feature. Commonly the urine was suggestive of pyelonephritis. Both are features of this case. Ninth: There were very unusual x-ray changes, characterized by increased density of bone (osteosclerosis) in essentially the same areas as have been described here, that is, increase in density of the bones at the metaphyseal margins, a circular increase in density of the periphery of the tarsal bones, and increased density at the base of the skull and also the bones of the spine and pelvis.

Finally, recurrent infections of one sort or another, including otitis media, have been present in this case as well as in the English cases.

There are additional features which have been reported to occur in "idiopathic hypercalcemia of infancy" but which were apparently not present in this child. First of all, hypercholesterolemia has been fairly common; second, the skull has been abnormally small, and, third, there have been marked hypotonia and muscle weakness. Striking mental retardation has also been reported but has been evident chiefly in older children after they have partially recovered from the disorder. Constipation has also been a prominent feature. However, even without these additional features I think that we have about 80 per cent of the typical findings of the syndrome in the present protocol.

Now, what is this disorder? What is its incidence? From Scotland it has been reported that, over a previous two-year period, roughly 5 per cent of admissions of children between the ages of 6 and 12 months were for this disorder. It was the fourth most common diagnosis made on the pediatric service in children of this age group. There was a total of fifteen cases in a population of 450,000. This gives us a rough idea of its incidence. In Great Britain, at least, it is not a terribly uncommon disease.

The etiology remains more obscure. I have indicated that it seems unlikely that this child had hyperparathyroidism. Such a possibility could not be absolutely excluded clinically. However, sufficient post-mortem material is now available to demonstrate quite adequately that the children with the clinical picture described here do not have parathyroid hyperplasia or adenomata, so that there is no support for the concept that this is hyperparathyroidism.

The two factors which do seem very striking are the intake of cow's milk rather than breast milk, and the fact that all these children did receive at least "normal amounts" of vitamin D. The point has been stressed that cow's milk contains four to six times as much calcium as an equal volume of breast milk. As a result, these children are receiving a very substantial amount of calcium in excess of that obtained in breast feeding, and they are receiving, usually, from 700 to 2,000 units of vitamin D. While these amounts are not considered excessive, it is of great interest that there is a striking difference between the vitamin D content of milk in England and that of milk here. The typical content of fortified milk here is 400 units per quart. The "national dried milk" used in England, which is apparently made available without cost to children under the age of 5 years, contains at least 1,400 units of vitamin D per quart as a minimum specification. Some workers have suggested that an important factor in the rather high incidence of idiopathic hypercalcemia in England and its apparent absence in the United States rests on the fact that the milk there contains between three and four times more vitamin D than does ours. Nevertheless, it is very difficult to call this disorder "vitamin D intoxication," since most of the children on similar intakes do not get into difficulty. It is tempting to postulate that in the particular group of children who do develop hypercalcemia there is a hypersensitivity to vitamin

D, and that a dose which is admittedly substantial but not enough to produce intoxication ordinarily is sufficient, in this group, to produce severe intoxication. Balance studies support this concept since they demonstrate an overabsorption of calcium from the gastrointestinal tract in children with idiopathic hypercalcemia. Instead of absorbing up to approximately 35 per cent of the dietary intake of calcium, these youngsters will absorb up to 60 per cent of their dietary intake. This excess absorption is quite characteristic of the effect of vitamin D and, incidentally, is also quite characteristic of the sarcoid patients who develop hypercalcemia. Indeed, it has been postulated that there is an abnormal sensitivity to vitamin D in such cases of sarcoid. While it is perhaps not proper to describe idiopathic hypercalcemia of infancy as a disorder resulting from vitamin D-calcium intoxication, the data strongly suggest that some special reaction to this combination of factors is a predominant feature in the development of this particular syndrome.

The clinical picture, in many respects, can best be explained as secondary to hypercalcemia. We know from experience in adults with hypercalcemia that anorexia, vomiting, and constipation are common, regardless of the etiology of the calcium disturbance. In such cases, muscle weakness and hypotonia are not uncommon and renal failure and hypertension occur very frequently. Increased incidence of systolic murmurs has not been reported in adults with hypercalcemia. However, it is of some interest that several of the children with idiopathic hypercalcemia and systolic murmurs have been found at post-mortem examination to have a peculiar calcification of the mitral rings. It may be that this calcification is responsible for the murmur, but this is by no means certain. The mental retardation also poses a problem. Craniostenosis has been suggested by some authors as the cause, but I think that remains an unsettled problem.

One notices, in reading the published autopsy protocols, that a number of these children had ulcers in the esophagus, and one or two had ulcers in the stomach at the time of death. I do not know whether this was a terminal phenomenon or not, but it is becoming increasingly evident that the combination of hypercalcemia and peptic ulcer is a very frequent one. We are sufficiently suspicious of hypercalcemia as an ulcerogenic agent that we measure serum calcium in any of our ulcer patients who do not respond promptly to treatment. I think we have turned up two or three previously unsuspected cases of hyperparathyroidism by this procedure. The combination of ulceration of the gastrointestinal tract and renal stones makes one even more strongly suspicious that there is underlying hyperparathyroidism.

I have not the vaguest idea about factors responsible for the change in the facies, and I hope that someone will comment on that. The susceptibility to infections is also something which remains obscure.

Many of these children have been thought to have pyelonephritis. The problem of diagnosing pyelonephritis has received a good deal of attention lately, and I think it is quite clear

that a routine urine culture without attention to colony counts does not comprise sufficient evidence to make a diagnosis of urinary tract infection. About 15 per cent of normal individuals will show a pathogen on culture of a clean voided urine. However, the counts in these normal subjects are almost always below 5,000 organisms per cubic centimeter and are usually below 1,000 per cubic centimeter. We have found that about 90 per cent of our diagnoses of pyelonephritis have evaporated since we started doing colony counts routinely. We place no reliance on cultures done without colony counts, because contaminants from the urethra are so common, even with the best cleansing procedure or with catheterization. Finding a pathogen on routine culture does not, in my opinion, provide adequate evidence for a diagnosis of pyelonephritis unless there are high colony counts (more than 100,000 organisms per cubic centimeter) or there are other clinical reasons for being certain that there is a urinary infection.

Now, what about the treatment of this disturbance? There have been four programs suggested for therapy: (1) a low calcium, low vitamin D diet; (2) cortisone; (3) chelating agents; and (4) sodium phytate.

To turn first to the low calcium, low vitamin D diet. This, on the basis of all the evidence, would seem to be the treatment of choice—at least, once the acute hypercalcemia has been brought under control. Low calcium milk can be given quite easily, I gather, and vitamin D can be withdrawn from the supplement and cereal without difficulty. There have been many instances of striking improvement in children placed on such a regimen. Cortisone has an even more dramatic and specific effect on the metabolic disturbance. As one gives cortisone to these children, the stool calcium increases very sharply and there is a return toward normal of the calcium balance, with only a very slight positive calcium balance consistent with growth. Within a matter of days, the serum calcium falls toward normal and the stool calcium increases. Unfortunately, if the cortisone is withdrawn the patients tend to relapse rapidly into their previous state. Since there are so many side effects from the cortisone therapy, it seems reasonable to use the drug chiefly to tide one over the acute situation, rather than as part of a long-range maintenance program. Chelating agents, which bind calcium and carry it into the urine, are not practical in the management of this disorder, since, in the amounts required, they almost uniformly produce vomiting, nausea, and diarrhea. Sodium phytate, so far as I know, has not been used extensively. This is a material which binds calcium in the gut and thus increases fecal calcium excretion. On theoretical grounds, and on the basis of studies by Dr. Philip Henneman at the Massachusetts General Hospital on several patients with sarcoid, sodium phytate administration would seem to be a feasible approach to preventing excessive calcium absorption.

What of the prognosis? Initially a division was made between a "benign" and a "malignant" form of the disorder. Now that dividing line seems to be disappearing as more and more cases are studied which seem to fall into an intermediate group. The major factor in prognosis seems to be

the severity of the renal lesion, just as in all hypercalcemic disorders. If the renal lesion is far advanced, the patient goes on to progressive renal failure and death. If the renal lesion is minimal and there is a return of function, then there is no reason why the patient should not survive and get along well for many years. On review of the reported cases it looks as if this difference applies in the group with "idiopathic hypercalcemia of infancy" as in all other hypercalcemic disorders. This is certainly not a benign disorder, for as many as one-third of the patients in some series have died. On the other hand, some children show a spontaneous recovery six months or a year after the diagnosis, even without treatment—the one serious sequela being mental retardation. This sequela has been almost uniform, even in the children who have shown a return to essentially normal renal function.

Finally, it is stated in the protocol that various biopsies were done. I would venture to say that in the kidney biopsy we will find, perhaps grossly and quite certainly microscopically, evidence of calcium deposition—that is, nephrocalcinosis. Secondary to this there will likely be disorder of the histology of the cortex, perhaps narrowing of the cortex, atrophy of glomeruli on an ischemic basis, some cellular infiltration, and tubular dilatation. The rib (presuming that it was biopsied at a site of the increased density) might be expected to show sclerosis. I do not know what to expect in the liver biopsy. So far as I can determine, there is nothing characteristic about the liver in this disorder.

One of the recent papers in the Lancet[1] was introduced with two brief statements, one by an editor of the Lancet and one by Dr. Edwards A. Park, of Baltimore, both statements having appeared within a year of each other (1953 and 1954). I think that they neatly and succinctly sum up the problem as it now stands. The editor of the Lancet comments: "Idiopathic hypercalcaemia. . . . Is this the price we pay for the abolition of rickets?" Dr. Park says, "In spite of the knowledge of the preventive action of vitamin D and also of ultraviolet light, rickets remains, in the Baltimore community, an extremely common disease."

DR. E. B. D. NEUHAUSER.—From the x-ray examination alone, I think the diagnosis of idiopathic hypercalcemia could be made, or very strongly suspected. In the films of the skull, the capacity of the vault appears to be quite normal in this child. His fontanel is perhaps smaller than one would expect at 9 months, and the sutures lack their normal prominence, but these are borderline changes. There is a very definite amorphous increase in the density of the bones at the base of the skull, and this may be present to a small degree in the bones of the vault (Fig. 1). The long bones have a normal diaphyseal architecture but in the spongiosa of the metaphyses the trabeculae are definitely increased in density, as are the epiphyses (Fig. 2) and the secondary ossification centers. The latter have rather punctate amorphous central areas. There is nothing to suggest rickets or a cortical bone resorption. This is, to us,

a rather unique appearance. I cannot think of many other conditions that would look like this. We once had a patient who had far-advanced tuberculosis and who was given massive doses of vitamin D, whose skeletal roentgenograms were similar to

Fig. 1.—Roentgenogram of skull. There is marked increase in density at the base of the skull.

this. Another patient, from the University of Vermont, with glycogen storage disease and renal damage, also had similar changes. There is a high association in our series of such bony lesions and severe hyperthyroidism. I believe this condition is not uncommon in the United States, but we have been overlooking it, I know. I have seen, personally, ten such cases from our own files and from films sent here from other areas.

DR. JOHN M. CRAIG.—Do you think this roentgenographic appearance of the bones is diagnostic?

DR. NEUHAUSER.—It is quite unique and should lead to a presumptive diagnosis.

DR. CRAIG.—Dr. Cohen, would you like to say a word?

DR. JONATHAN COHEN.—Some of the problems of the incidence of this disease have been studied by the Medical Research Council in England very recently. This study revealed that the vitamin D content of many of the children's diets was greatly increased.

Fig. 2.—Roentgenogram of femora, showing marked changes in the bony architecture.

Since vitamin D will deteriorate very rapidly, the manufacturers of dried milk and foodstuffs were putting a larger amount into the milk and other food than was absolutely indicated, so that the children in England were getting perhaps 3,000 units a day, or even more, depending upon how much of these foods, plus the added supplements, they were receiving.

DR. NEUHAUSER.—I do not think one can always invoke vitamin D intoxication in such instances. The first such patient that I saw, about five years ago, was sent up from Johnson

City, Tennessee—a little child from the hills, who never received extra vitamins.

DR. CRAIG.—Dr. Schwartz accurately predicted what we would find in the kidney. This is a section of the kidney (Fig. 3), which was taken to include the capsule and as far down as the surgeon dared to get into the medulla. Characteristically, there is marked destruction of the renal parenchyma in the subcortical area, with marked tubular atrophy. The tubules contain casts and there is a good deal of inflammatory reaction in the immediately surrounding tissue. There are few cellular casts, and it is difficult to say for certain that this represents pyelonephritic involvement. Crystalline material is present in the cortical portion and this is more marked in the outer medulla. This material takes a basophilic stain, though we were unable to demonstrate, by the von Kossa technique or by Perls' reaction, the presence of phosphate or iron. This may, perhaps, have been due to the acid fixation used, which might leach out that material. Thickening of the basement membranes and hyaline scarring of the glomeruli are not marked features in this case, although there is minimal focal thickening of the Bowman capsule of the tubular membranes. In the shaft of the rib there is a tremendous cortical thickening (Fig. 4), with fairly recently deposited bone which is laid down over the old cortical bone and gives the marked increase in density that is seen on x-ray. In the costochondral junction of the rib an unusual change for a child of this age is the persistence of the cartilage columns at a considerable distance away from the actual growth zone (Fig. 5). This is a normal finding in premature babies but would not be found in a normally growing child of this age.

Dr. Reginald Lightwood originally was of the opinion that there were two different forms of this syndrome. One, he feels, is secondary to the socioeconomic public health measures related to an increased vitamin D and calcium intake. This group tended to do well, the condition was transient and benign, and most of them recovered. They had normal facies, no hypertension, no cardiac murmur, and no osteosclerosis. A small number of them had renal acidosis but their serum levels were similar to those of the next group, which showed what has been referred to as the Fanconi-Schlesinger syndrome. Dr. Fanconi, from Switzerland, and Dr. Schlesinger, from England, wrote an article together in 1952 concerning the second form of hypercalcemia of infancy. They thought that it represented an effect of a congenital metabolic disorder and that it should be distinguished, as Dr. Lightwood indicated, from that form of hypercalcemia which is due to excessive calcium and vitamin D. In this second group, the condition was much more severe. Many of them have permanent mental retardation, a characteristic physiognomy, hypertension, and hypercholesterolemia. Dr. Lightwood has indicated several transition forms between the two types. I think that it will be interesting, as we go along, to see whether, eventually, the two groups will become more distinct, or whether,

Fig. 3.

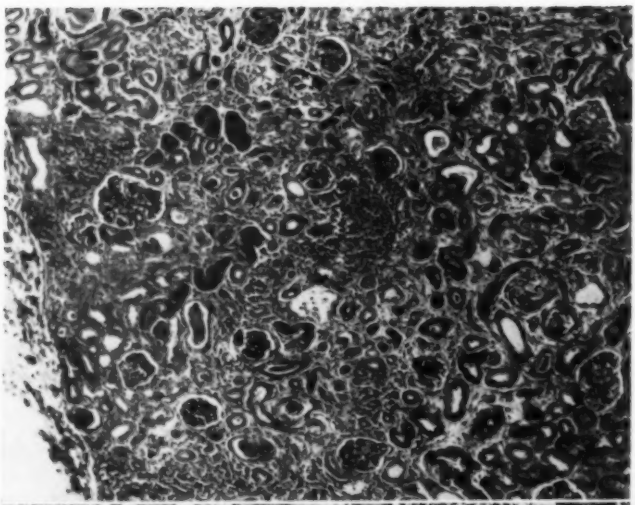
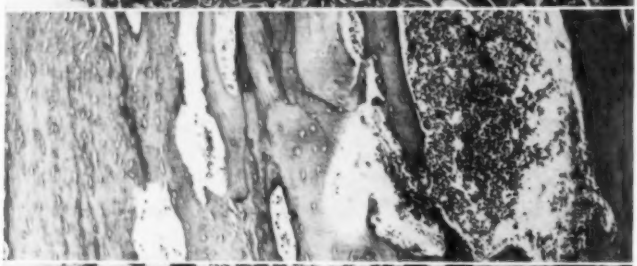


Fig. 4.



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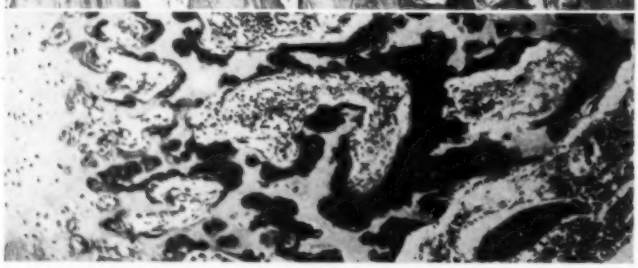

Fig. 3.—Photomicrograph, kidney. The subcapsular cortical zone has many atrophic tubules with partially scarred glomeruli and an interstitial lymphocytic infiltrate. (Toluidine blue and eosin; ×145; reduced ¼.)

Fig. 4.—Photomicrograph, rib. The cortical bone in the shaft is greatly thickened, with little evidence of remodeling of bone. (Hematoxylin and eosin; ×110; reduced ¼.)

Fig. 5.—Photomicrograph, rib. The zone of provisional calcification shows a remarkable persistence of cartilage matrix. (Hematoxylin and eosin; ×110; reduced ¼.)

as Dr. William Schwartz suggests, they will merge into one group.

DR. ROBERT SCHWARTZ.—Dr. Peter Auld is following this child and another such child. These diagnoses were originally made by Dr. Neuhauser, and the men on the service were somewhat chagrined by this unsuspected diagnosis. We have been trying to get some calcium-free milk for both of these children and have been in contact with several baby food producers, but we have been unsuccessful to date in obtaining a calcium-free formula for these two families. The first child has been on sodium phytate for about five months.

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Medical Progress

HEMOPHILIA

ARTHUR E. MCELFRESH, M.D.
PHILADELPHIA, PA.

THE increased understanding of the mechanisms responsible for the coagulation of blood has changed the concept of hemophilia from that of a single disorder to one in which deficiencies of one of several factors may produce the same clinical picture. The situation has been further complicated by the use of different names to identify the same coagulation factor (Table I).

A simplified but adequate concept of coagulation is illustrated in Table II.[1-4]

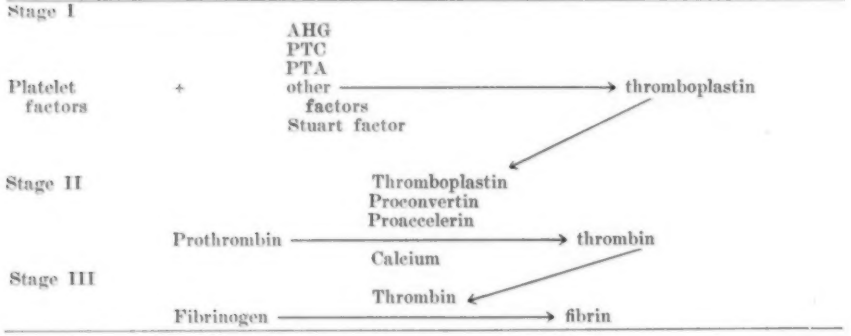
The first stage involves the formation of thromboplastin from platelet

TABLE I. COAGULATION FACTORS AND THEIR SYNONYMS

ANTIHEMOPHILIAC GLOBULIN (AHG)	PLASMA THROMBOPLASTIN COMPONENT (PTC)	PROCONVERTIN	PROACCELERIN
Antihemophiliac factor Factor VIII	Christmas factor Factor IX	Stable factor Factor VII Convertin serum prothrombin conversion accelerator (SPCA)	Labile factor Factor V Ac-globulin

The names given at the top are those most commonly used in this country.

TABLE II



From St. Christopher's Hospital for Children, and the Department of Pediatrics, Temple University School of Medicine.

factors, antihemophiliac globulin (AHG),[5] plasma thromboplastin component (PTC)[6-11] and other factors.[1] Although plasma thromboplastin antecedent (PTA)[12-14] is shown as participating in the formation of thromboplastin, the evidence for this is not complete. Thromboplastin then initiates the conversion of prothrombin to thrombin; this reaction requires calcium and is accelerated by proconvertin and proaccelerin. Finally, fibrinogen is converted to fibrin in the presence of thrombin. In addition to these factors, the action of the platelets in producing clot retraction and the importance of a normal vascular bed must be borne in mind. The level of any single factor involved in coagulation must be quite low before symptoms appear, since there are greater quantities of these factors than are normally needed.

TYPES OF HEMOPHILIA

The name hemophilia should be reserved for deficiencies of factors involved in the first stage of coagulation. There are now three accepted types of hemophilia which are fairly common; they result from the deficiencies (1) of antihemophiliac globulin (AHG), (2) of plasma thromboplastin component (PTC), and (3) of plasma thromboplastin antecedent (PTA). In addition, several other less common types have been described, such as Hageman factor deficiency[15, 16] and the Stuart factor deficiency.[18, 19] The three main types will be described at some length and the rarer forms only briefly.

Deficiency of Antihemophiliac Globulin.—The most common type of hemophilia, as well as the first to be described, results from a deficiency of antihemophiliac globulin (AHG), a protein which participates in the formation of thromboplastin. AHG is short-lived both in vivo and in vitro; it lasts only 8 to 12 hours in the body. It is labile in stored oxalated blood, having a half-life of only 8 to 10 hours, but it is quite stable in blood carefully drawn in a citrate solution. It is consumed during coagulation and is virtually absent from serum. Hemophilia resulting from a deficiency of AHG is a sex-linked disorder. The gene is carried by females and is inherited by one half of their children. One half of the female children will be carriers, whereas one half of the male children will have the disease. The remaining children will be entirely free from the affected gene. It is probable that there are several alleles of the gene responsible for this condition since the level of AHG in any given hemophiliac may vary from 0 to 15 per cent of normal,[20] and since there is considerable variation in the severity of the symptoms among different patients. Seventy-five to 80 per cent of all hemophilia is the result of a deficiency of AHG.[21, 22]

Deficiency of Plasma Thromboplastin Component.—In 1952 Schulman and Smith,[8] and White and Aggeler[6, 7] in this country and Biggs and associates[9] in England described patients with the clinical picture and laboratory findings of hemophilia whose blood corrected the defective coagulation of other hemophiliacs. These patients, therefore, were not deficient in the same factor as the usual hemophiliac. White and Aggeler called the deficient factor "plasma thromboplastin component"

(PTC) while Biggs gave it the name of the person in whom it was first found to be absent, i.e., the "Christmas factor." In this country the term PTC has become the preferred term. PTC is a protein which unlike AHG is stable on storage, persists in the body for two to three days, is not consumed during coagulation, is present in serum, and is adsorbed from plasma or serum by incubation with barium sulfate or aluminum trisilicate. It probably combines with a platelet factor to form one of the first stages in the formation of thromboplastin. As is the case with deficiency of AHG, deficiency of PTC occurs only in males and is the result of a sex-linked recessive gene inherited from females. It is probably formed in the liver, is depressed in some disorders of the liver, is reduced by some coumarin drugs,[24] and is present in reduced amounts in the blood of newborn infants.[25] Deficiency of PTC accounts for approximately 15 per cent of the patients with hemophilia.[21, 22]

Deficiency of Plasma Thromboplastin Antecedent.—Plasma thromboplastin antecedent (PTA) was described by Rosenthal[12] in 1953, who demonstrated that plasma from a person with a prolonged clotting time corrected the abnormal coagulation of blood deficient in AHG or PTC. PTA is present in both plasma and serum, is stable on storage (it may actually become more active), and is for practical purposes not adsorbed by barium sulfate. Clinically, PTA deficiency is the mildest of the three forms.[13, 14] In contrast to deficiency of AHG or PTC, the manifestations of which are variable in intensity but usually associated with spontaneous hemorrhages, symptoms of PTA deficiency may not appear until the patient undergoes tonsillectomy, extraction of a tooth, or some other surgical procedure. For this reason all members of the patient's family should be studied to discover asymptomatic persons with this disorder.

OTHER FORMS OF HEMOPHILIA

Hageman Factor Deficiency.—A deficiency of a thromboplastin factor has been described by Ratnoff[15] as the Hageman factor. This deficiency results in a prolonged coagulation time and in deficient prothrombin consumption, but persons with this deficiency have no symptoms and have even been operated upon without excessive bleeding. This deficiency also has been confirmed by other workers.[16]

Stuart Factor Deficiency.—A deficiency of a factor which appears to be similar to proconvertin but which is also involved in thromboplastin formation has been described as the "Stuart factor."[18, 19] This factor has considerable theoretical interest; however, the relative frequency of Stuart factor deficiency is not yet known. The symptoms would appear to be mild.

Deficiencies of several other serum factors have been described; at the present time, however, these factors are not well enough accepted to allow one to form an opinion as to their frequency or ultimate importance.

Vascular Purpura With AHG Deficiency.—A combination of deficiency of AHG and vascular purpura has been reported.[23] This syndrome is characterized by a prolonged bleeding time as well as by a prolonged clotting

time and deficient prothrombin consumption. This variant of vascular purpura has occurred in females and must be inherited in some fashion other than that of the usual sex-linked deficiency of AHG. It may be more common than presumed, since deficiency of AHG has not usually been sought in females.

The differential diagnosis of these less common types is complicated; however, they may be suspected in females who seem to have hemophilia or in very mild hemophiliacs.

DIAGNOSIS

The diagnosis of the usual varieties of hemophilia is not difficult. In both AHG and PTC deficiency there is often a history of bleeding at the time of birth, either from the umbilical cord or from circumcision. If these symptoms are not present, there may be a period of six months or so before bruises are appreciated owing to the relatively atraumatic existence of the infant during this period. Bruises then occur which are excessive both in number and in size. A history of hemophilia in the family is frequently not elicited, in part owing to the inability of many American families to secure correct information about their family trees beyond one or two previous generations. The studies required to establish the nature of the disorder are relatively simple; most can be performed by routine hospital laboratories. We have listed them below as we routinely perform them. Only the prothrombin consumption test will be described in detail. The thromboplastin generation test will not be described since it is a more complicated procedure which usually need not be performed and which should, for technical reasons, best be used only by persons experienced in the study of coagulation.

1. *Clotting Time.*—The determination of the clotting time is valid only when venous blood is used. The blood should be secured with a two-syringe technique in order to reduce the possibility of contamination of the specimen with tissue fluid. The blood from the first syringe may be used for the determination of the prothrombin time; that obtained in the second syringe is then used for the determination of the clotting time according to the three-tube Lee-White method. We consider twelve minutes to be the upper limit of normal when the test is performed in glass tubes. The test is abnormal in almost all forms of hemophilia. The capillary tube method utilizing capillary blood is to be condemned for it will sometimes yield normal values in the presence of hemophilia and may be prolonged in a normal person during hot, moist weather.

2. *Bleeding Time.*—The Ivy method using a 2 mm. puncture performed on an avascular area of the forearm with a blood pressure cuff placed above the elbow and inflated to 40 mm. Hg is the preferred method. A word of caution is necessary regarding the performance of bleeding time determinations from the ear lobe since continuous hemorrhage may occur from this site when the bleeding time is prolonged, and it is difficult to apply pressure to this area. The bleeding time is normal in hemophilia.

3. *Prothrombin Time.*—The one-stage prothrombin time is adequate for the detection of deficiencies of prothrombin, proconvertin, proaccelerin,

and the Stuart factor. Since thromboplastin is supplied to the mixture in the performance of this test, the test is normal in all forms of hemophilia.

4. *Prothrombin Consumption.*[4, 26]—The prothrombin consumption test is simple to perform and has a diagnostic accuracy exceeding that of the simple clotting time; it may frequently be abnormal in the presence of a normal or borderline clotting time determination. The test is based upon the fact that coagulation of normal blood results in the consumption of most of the prothrombin present; when measured one hour after clotting there is virtually no prothrombin left in the serum. In hemophilia, since thromboplastin formation is deficient, utilization of prothrombin is poor and abnormal amounts remain in the serum. The test is performed by adsorbing prothrombin from normal plasma by barium sulfate; 50 mm. of barium sulfate are added to each milliliter of plasma and the mixture is incubated at 37° C. for 20 minutes. This technique also removes PTC and stable factor but they are not involved in the test. The barium-sulfate-adsorbed normal plasma is mixed with an equal amount of serum obtained one hour after clotting from the suspected person, and a one-stage prothrombin time determination is performed on the mixture. The only source of prothrombin in this mixture is that which remains in the serum of the suspect; a prothrombin time of less than 25 seconds indicates that there is a greater amount of prothrombin than normal in the serum and is indicative of some form of hemophilia if the platelets are normal. To demonstrate the feasibility of this test we have adsorbed prothrombin with the impure barium sulfate commonly used as a contrast medium for roentgen studies and have obtained good results. Since almost all laboratories can perform one-stage prothrombin determinations, there is little excuse for this test being unavailable.

DIFFERENTIAL DIAGNOSIS OF TYPES

AHG is present only in fresh plasma; PTC is present in fresh or stored plasma and serum; PTA is present in fresh or stored plasma, serum, and serum adsorbed by barium sulfate. These properties allow the differential diagnosis to be accomplished by noting the correction produced upon the clotting time and the prothrombin consumption by the addition of small amounts of these substances to the blood of the suspect.

TABLE III. ANTIHEMOPHILIAC FACTORS PRESENT IN PLASMA AND SERUM*

	AHG	PTC	PTA
Fresh plasma	+	+	+
Aged serum	-	+	+
Aged serum adsorbed with barium sulfate	-	-	+

*The appropriate use of these components of blood makes it possible to determine the type of hemophilia in a particular situation (Table IV).

Reference to Table III will make this clear. In the procedure used to ascertain the type of hemophilia, 0.1 ml. of plasma is placed in each of three tubes, a similar amount of serum in three tubes, and the same amount of serum adsorbed by barium sulfate in three additional tubes. A series of three tubes also contains 0.1 ml. each of saline; this is the control series. Twelve milliliters of blood is then obtained from the patient and 1 ml. is added to each tube; all tubes are inverted once and the clotting time

determined. The prothrombin consumption is then performed on the serum from one tube in each series. A sample protocol is shown in Table IV to illustrate the results in a patient with PTC deficiency.

TABLE IV. A SAMPLE PROTOCOL SHOWING THE RESULTS OBTAINED IN THE TEST TO DIFFERENTIATE THE TYPES OF HEMOPHILIA*

SUBSTANCE ADDED TO TEST BLOOD	CLOTTING TIME (MIN.)	PROTHROMBIN CONSUMPTION TIME (SEC.)
1. 0.1 ml. saline	36.0	13.0
2. 0.1 ml. fresh plasma	14.6	42.0
3. 0.1 ml. aged serum	13.8	41.0
4. 0.1 ml. aged serum adsorbed with barium sulfate	34.0	13.8

*The patient is deficient in PTC. There is correction of both the clotting time and the prothrombin consumption of the patient's blood by plasma and serum but not by serum adsorbed with barium sulfate.

This method usually suffices to determine the type of hemophilia in patients with severe manifestations. However, the Stuart factor has the same characteristics as PTC in regard to its presence in plasma and serum and its adsorption by heavy metals such as barium. Deficiency of Stuart factor, however, is also manifested by a prolonged prothrombin time.

If there are only mild symptoms, cross-correction studies are desirable between the plasma or serum of the unidentified hemophiliac and blood of persons known to be deficient in each factor. Occasionally clear-cut results may only be obtained from the thromboplastin generation test.

THERAPY

Therapy falls into three categories: local, specific replacement of deficient factor, and educational.

Local Therapy.—Local therapy is often sufficient to arrest minor hemorrhage; the parents should be educated in its application as soon as the diagnosis is made. The use of cold packs, pressure or elastic bandages, or of Gelfoam and thrombin is often all that is required when the hemorrhagic area is accessible. In the therapy of large ecchymoses of the soft tissues of the extremities temporary immobilization by bed rest, traction or splinting is of value. In dealing with hemorrhage into the soft tissues, however, the benefit to be obtained by rest or splinting must be weighed against the disadvantage of time lost from school and the emotional trauma to the child. We have often compromised by using a plaster shell or Buck's extension at night and allowing the child to attend school during the day with elastic bandages exerting pressure on the ecchymotic site. Large ecchymoses into muscles may cause considerable pain and spasm; occasionally residual tightening of the muscles may require gentle physiotherapy.

Specific Therapy.—Specific therapy requires replacement of the specific absent factor; at present this can only be accomplished intravenously. The requirements for replacement vary with the type of hemophilia. Since AHG persists only eight to twelve hours in vivo, replacement of AHG must be given frequently. Although AHG is quite labile in oxalated blood, it is rather more stable in citrate[27]; we have produced a marked reduction in clotting time and prothrombin consumption by infusing 7-day-old citrated plasma. It is preferable, however, to use fresh plasma or plasma which has been

freshly frozen. Five to ten cubic centimeters per kilogram yields approximately 10 per cent concentration and may be used for the initial administration. Ideally, the clotting time and/or the prothrombin consumption should be measured following the administration; in small children this may not be feasible. When the degree of correction desired has been demonstrated to have been obtained from a given amount of plasma, such an amount may be repeated every eight to twelve hours without securing subsequent measurements. PTC is more stable; one administration of 5 ml. per kilogram corrects the hemorrhagic tendency for two to three days. PTA deficiency does not usually require specific replacement with plasma; however, when needed, as for surgery, the benefit from one plasma infusion persists for two to three weeks.

Some occasions always require specific replacement. Surgery is to be avoided whenever possible in patients with hemophilia but, if necessary, replacement of the deficient factor should begin prior to, be continued during, and be maintained for at least 48 hours after the operation. Even with the use of this regimen, bleeding may occur seven to ten days later, particularly in AHG deficiency. Free bleeding from lacerations may require specific replacement as may renal hemorrhage or hemorrhage into the tissues of the pharynx or lower airway during respiratory infections. Most commonly, particularly in AHG and PTC deficiency, hemorrhage into the synovial sacs of the joints is the indication for specific replacement. Deformity may occur following one such hemorrhage; more commonly there is no limitation of motion following the first episode, but repeated insults lead to intracapsular scarring, limitation of motion, and disability from the development of a hemarthrosis. Therapy for such bleeding must be vigorous. Replacement therapy should be given immediately, and the affected part should be immobilized as soon as a joint appears to be involved; we prefer to use one half of a bivalved plaster shell with the extremity held therein by elastic bandage. This arrangement allows for observation and application of cold packs to the joint and avoids the possibility of circulatory embarrassment from further swelling. Ideally, the immobilization should be continued for four to six weeks or until all blood has been resorbed and the joint is of normal size; in some patients with frequent intra-articular hemorrhages this is not practical and motion may be resumed when the pain and spasm have disappeared. The value of removing blood from the joint space is not established. We are currently employing this procedure after first ascertaining that the administration of suitable blood or plasma has reduced the clotting time and prothrombin consumption to normal. There is apparently no value in injecting hyaluronidase intra-articularly, but the instillation of 25 to 50 mg. of hydrocortisone into the joint may be of some value. Whether or not the aspiration of blood and introduction of hydrocortisone will be of any benefit in preventing deformity remains to be assessed; however, the removal of

blood is dramatically effective in relieving the severe pain which accompanies massive hemorrhage into joints. Despite early and adequate medical and orthopedic care, it is impossible to prevent some degree of hemarthrosis from developing in the majority of severe hemophiliacs.

General Measures.—The care of the hemophiliac requires more than the measures outlined for the treatment of bleeding. Prophylactic dental care is essential since the problems involved in the extraction of teeth are great. The pediatrician should impress the need for proper oral hygiene upon the family and help them find a cooperative dentist who understands the problem. Routine immunizations should be administered inasmuch as the slight possibility of bleeding from the needle puncture is more than outweighed by the benefits provided by the immunization.

The physician must also counsel the parents on the multitude of emotional problems which may develop. He must recognize and attempt to assuage the mother's sense of guilt and must caution against maternal overprotection of the child, for the threat of hemorrhage often allows the child to control the entire family. Since contact sports or even games such as tennis are forbidden most hemophiliacs, we have found it useful to encourage the fathers to learn sports in which the hemophiliac child may participate, such as fishing, riflery with small caliber guns, miniature golf, and swimming. The possession of a pool or billiard table helps assure the older hemophiliac of acceptance by his contemporaries despite his inability to engage in the usual outdoor activities. The older hemophiliac is usually the best judge of what activities cause him distress and he may be allowed some latitude in the selection of his activities.

The physician must also explain to the parents the genetic implications. As in all genetic counseling, he must leave the decision regarding future children to the parents since this is influenced by their religion, social and economic status, and emotions and not alone by medical considerations.

Finally, the parents should be encouraged to join a local chapter of the Hemophiliac Foundation. The exchange of experiences and the comfort of sharing one's trials plus the opportunity of working to support the projects of this organization give the parents, and often the patient himself, a needed outlet for their anxiety.

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Comments on Current Literature

MUMPS VIRUS AND SUBACUTE THYROIDITIS

SUBACUTE thyroiditis has distinctive clinical and pathologic features by which it can be differentiated clearly from acute pyogenic infections of the thyroid, such as those caused by hemolytic streptococcus, staphylococcus, pneumococcus, etc., and from the forms of chronic thyroiditis described by Reidel and Hashimoto. While the exact etiology of subacute thyroiditis is unknown, both the clinical manifestations and the pathologic observations have led to the general consensus that a viral agent, as yet unidentified, is probably responsible. An excellent review by Hazard[1] in 1955 included a detailed classification differentiating the various forms of thyroiditis with a discussion of clinical and laboratory findings, pathogenesis, treatment, and course for each.

Subacute thyroiditis is an inflammatory disease involving the thyroid gland which is usually associated with a systemic reaction characterized by fever and general malaise. The nonsuppurative form of thyroiditis resolves in about fourteen days, and deaths are not common. Disturbance of thyroid function is temporary, as a rule. On the other hand, the suppurative type of thyroiditis carries more serious import, and convalescence may be stormy and prolonged. In one reported series, nine of forty-one patients died, and where gangrene of the thyroid occurred, the disease was fatal invariably. Extension from the thyroid to other tissues is a frequent finding: into the trachea or esophagus, or into the mediastinum.[1] Suppurative thyroiditis may be recurrent, and there may be widespread destruction of the gland with consequent disturbance of thyroid function.[2] Direct cultures have been obtainable where there was suppuration and drainage. According to Hazard, the "organisms most commonly reported are *Streptococcus hemolyticus, Staphylococcus aureus,* and pneumococcus. Other organisms that have been recovered are: *Salmonella typhosa, Hemophilus influenzae, Escherichia coli, Salmonella paratyphi.*"[1] Attempts to recover an infectious agent from biopsy tissues in the case of the nonsuppurative type of thyroiditis have been without success.

Within the past few years a comparatively large number of cases of the nonsuppurative form has been seen in Israel, affording an opportunity for viral studies and further search for a possible viral agent, or agents. Results of these investigations are reported by Eylan, Zmucky, and Sheba[3] in the British journal, *Lancet,* for May 25, 1957. Fifteen patients with subacute thyroiditis are included in this study.

The illness usually began with anorexia, general malaise, and low-grade fever, accompanied by pain radiating from the neck to the ears which was more noticeable on swallowing, or was initiated by swallowing. Swelling and tenderness of the thyroid gland, either unilateral or bilateral, appeared within two to three days thereafter. Tachycardia and sweating were prominent findings, and in a number of instances the eyes had a staring expression. Some patients complained of abdominal discomfort, in spite of absence of abnormal physical signs. In eleven of

the fifteen patients in this series reported by Eylan, Zmucky, and Sheba, the disease was not left to its natural course, since these eleven received cortisone or corticotropin. As has been observed generally, steroid therapy brought about prompt reduction in glandular swelling with complete disappearance of detectable thyroid enlargement in about seventy-two hours. Temperature usually returned to normal within twenty-four hours following such treatment. In seven of the ten patients treated, the pyrexia and painful swelling of the gland recurred after steroid medication was discontinued.

Metabolic and hematologic studies were carried out in detail on the majority of these patients and in the case of some, long-term follow-up was possible. "A mild polymorph leucocytosis (up to 17,000 per c.mm.) was observed in three-quarters of the cases. The erythrocyte-sedimentation rate was usually raised, above 50 mm. in 1 hour (Westergren) in 11 of 15 cases. The serum-P.B.I. level was above 8 micrograms per 100 ml. in 8 of 11 cases in which it was estimated. In contrast, the uptake of radio-iodine was greatly reduced in 12 of 15 cases. The combination of a high P.B.I. and low radio-iodine uptake is regarded by most observers as characteristic of subacute thyroiditis."[3] Ten of the patients were followed for six months or longer with repeated I^{131} and protein-bound-iodine studies; after six months at the longest, all had returned to the euthyroid state, and none developed hypothyroidism or hyperthyroidism.

In the case of four of these patients biopsy was performed and, in all four, histologic study of the excised tissue revealed invasion by inflammatory cells. In two instances in which biopsy was obtained early in the course of the disease, polymorphonuclear cells predominated, while lymphocytes were the predominating cells in the two instances in which the biopsy tissue was obtained late in the course of the disease. All four biopsy specimens showed evidence of marked disruption of the normal thyroid acinar pattern. Many giant cells were present, an observation interpreted by the authors as evidence of destroyed acini.

Attempts to recover a viral agent from the blood and from fecal specimens were without success. However, in two of the four cases in which biopsy was performed, an infective agent which was Seitz filter passing and which is thought to be identical with the virus of mumps, was recovered from excised thyroid gland tissue. Appropriately prepared tissue specimens were inoculated into mice, adult and newborn hamsters, and by yolk sac route into embryonated eggs of eight days' incubation. Results of the animal inoculations were negative except in the case of suckling hamsters. In a proportion of these young animals signs of encephalitis were apparent within six to nine days following inoculation of tissue preparations from two of the patients. Passage of the infective agent was established readily, and the virus was identified tentatively as a strain of mumps virus. With reference to the embryonated eggs inoculated, the procedure employed is of interest. Initially tissue preparations were inoculated into the yolk sac, followed in five days by blind passage of yolk sac suspension to the amniotic cavity of fresh embryonated eggs. Five days later amniotic fluid withdrawn from the passage eggs was found capable of agglutinating human type O red cells. This hemagglutination, indicating the presence of virus, was prevented by the addition of serum from patients convalescent from classical mumps, and by the addition of serum from the patients recovering from subacute thyroiditis. Random sample control sera did not prevent the hemagglutination phenomenon at all, or suppressed it only to a very insignificant degree. Positive complement fixation tests were obtained in ten of eleven patients followed in this respect, which on comparison with an adequate number of controls from the general population,

are considered by the authors as significant evidence of recent contact with the virus of mumps.

The authors believe that the subacute thyroiditis in these particular patients was caused by a strain of mumps virus. This virus is known to have an affinity for glandular tissue: salivary, testicular, pancreatic, ovarian, mammary tissue, etc. While no simultaneous enlargement of salivary glands was observed in the patients of this series, a number of them did complain of abdominal pain, and in three of six instances in which enzyme studies were carried out, there was a rise in blood diastase above 200 Somogyi units. During the period when these cases of subacute thyroiditis were being observed, the incidence of mumps was unusually high in Israel, the rate having risen from 12 per 10,000 population in 1953 to 32, and 44 per 10,000 population in 1955 and 1956. In the case of the earlier patients in the series, no inquiry was made as to the history of contact with mumps; in the later cases, however, inquiry was made specifically, and four of the later patients admitted recent close contact with persons suffering from classical mumps, in some instances members of the immediate family.

The clinical and pathologic findings noted in certain types of nonsuppurative thyroiditis have suggested viral etiology, and these objective studies reported by Eylan and his associates, isolation of the virus of mumps from excised thyroid tissue and demonstration of antibody response, tend to support this impression.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

The subject of continuing medical care has appeared in recent articles on medical education as if it were something new. We pediatric nurses and physicians have been practicing it for the past forty-six years,[1] and it is high time that those in adult nursing and medicine, as well as in geriatrics, give us credit for discovering the value of this program, and followed our example.

About 1911, some American consulting pediatricians began providing comprehensive care for children as a *secondary* activity, in addition to their consultation practice, e.g., Fife and Sinclair in Philadelphia, and Saunders, Zahorsky, and Tuttle in St. Louis, among others.[2] This trend was gradually rising before the First World War, but spread more widely after it. Perhaps part of the impetus was the experience with French puericulture gained by the younger consulting pediatricians sent to France during the First World War by the American Red Cross to help with the care of the French war orphans. Several other factors are also responsible for this change in American pediatrics from solo consultations to child care practice. For example, some consulting pediatricians recognized the need, demand, and market for systematic, periodic, supervised child care and made this field their *primary* occupation, rather than a sideline. J. H. Mason Knox was one of the leaders in changing pediatrics from the diagnosis and care of sick children to what we know now as comprehensive and continuing child care. He let it be known, early in his years of practice, that he would be glad to see well children for general health supervision. The idea of inviting visits from healthy children and charging for them was then so unorthodox as to be considered unethical, and the legend persists that there was outspoken professional sentiment against it.[3] Lucas in San Francisco, Royster in Norfolk, and others also commenced seeing children from birth to the age of two or three at frequent intervals, with advice to the mothers about feeding habits, growth, development, inoculations, and so forth, sometimes for a monthly or annual fee.[1]

"Well-baby" conferences were started before the First World War and the "Summer Round-Up" for children entering school was soon extended throughout the entire period of childhood.[4] The pediatricians early recognized that the environment is a potent influence on the life and welfare of the individual and they sought those elements in the environment which could be modified favorably, e.g., milk supply, school desks and lighting, poison sources, accident causes, etc., in order to avoid placing the individual at a disadvantage so far as health was concerned.[5]

Obviously teamwork is essential for comprehensive and continuing care. Physicians, nurses, psychologists, psychiatrists, dietitians, occupational and physical therapists, students of medicine and nursing, schoolteachers, scout leaders, and, last but not least, social workers all must unite and accept the total and continuing responsibility for the health of the individual or the family as a unit in order to keep children well from conception through adolescence. All of these workers must be interested in the child as an individual with personal, family, and environmental problems.

Equally obviously, any team, athletic or medical, needs a captain, and he or she should not be selected because of having an M.D., Ph.D. in Psychology, or M.S. in Nursing, but rather on the basis of having an instinctive love and understanding of children, and an ability, like that of Osler, to

make each patient feel that everyone on the team is primarily interested in his or her welfare.[6]

In our and other hospital outpatient departments most of these resources are, or should be, available, and most schoolteachers and scout leaders can be recruited for the program. For physicians in private practice, the city and county usually furnish the needed help if requested.

The most important factors are (1) the education of nurses, physicians, and the public in the need for this total care and in the value of teamwork,[6] and (2) a definite plan of continuing and progressive supervision in which the patient, the family, and the team participate and evaluate.

MILDRED M. SHERWOOD, R.N.
WILBURT C. DAVISON, M.D.
Department of Pediatrics
Duke University Medical Center
Durham, N. C.

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News and Notes

The **Society for Pediatric Research** elected the following officers for 1957-1958 at the meeting on June 19:

President: Dr. Edward L. Pratt, Dallas.

Vice-President: Dr. Alexander Nadas, Boston.

Secretary-Treasurer: Dr. Sydney S. Gellis, Boston.

Members of the Council: Dr. Robert A. Aldrich, Seattle; Dr. Robert Cooke, Baltimore; Dr. Wallace McCrory, Philadelphia; Dr. John Osborn, San Francisco; Dr. Robert Slater, Toronto; Dr. Clark West, Cincinnati.

Dr. Katharine Dodd has been appointed Distinguished Professor of Pediatrics, University of Louisville School of Medicine, effective August, 1957. Dr. Dodd is retiring as Chairman of the Department at the University of Arkansas, which she has served for the past five years. Previous to this, Dr. Dodd taught at the University of Cincinnati for nine years after teaching pediatrics at Vanderbilt for eighteen years. As Distinguished Professor, Dr. Dodd will be free of administrative detail and able to bring to bear her rich experience in the teaching of clinical pediatrics upon the undergraduate students and the twenty-one house officers of the Department.

Dr. Albert Dorfman has been made a full professor in the Department of Pediatrics of the Division of Biological Sciences of the University of Chicago. Dr. Dorfman recently was made director of the LaRabida University of Chicago Institute, University of Chicago. This Institute was recently established for patient care, teaching, and research at LaRabida Sanitarium, now an affiliate of the University of Chicago.

The **New York Medical College Metropolitan Medical Center** announces a postgraduate course in the *Contagious and Communicable Diseases* under the direction of Dr. Harold Abramson, Professor of Clinical Pediatrics, Nov. 6. 1957, to May 28, 1958, thirty sessions, Wednesdays, 10 A.M. to 3 P.M. For information apply to Office of the Dean, New York Medical College, Fifth Avenue at 106th Street, New York 29, N. Y.

The program of the fourth annual meeting of the **Academy of Psychosomatic Medicine,** to be held Oct. 17-19, 1957, at the Morrison Hotel in Chicago, will be devoted to "Psychosomatic Aspects of Obstetrics, Gynecology, Endocrinology and Diseases of Metabolism." Information may be obtained from Dr. William S. Kroger, Secretary, 104 S. Michigan Ave., Chicago 3, Ill.

The following courses for 1958 have been approved by the **International Children's Centre** in Paris:

Course on day and residential nurseries, January 6-26.

Course on mentally defective children, January 27—March 2.

Course of Social Pediatrics (Dakar), February 24—April 4.

Course on Tuberculosis in the Child (in French and in English), March 3-30.

Course of Social Pediatrics, April 14—July 6.

Course on Nutrition, September 15—October 12.

Course on Maternal and Child Welfare for social and administrative personnel, October 13—December 20.

Maternal and Child Welfare training course for African midwives (Dakar).

For any additional information, apply to Public Relations Service, Château de Longchamp, Bois de Boulogne, PARIS-XVI^{e}.

The **Pediatric Department of the School of Postgraduate Medicine at City of Hope Medical Center,** Duarte, California, announces a two-day course on "Hereditary Diseases in Children," Saturday and Sunday, Oct. 12 and 13, 1957, under the auspices of the City of Hope Medical Center. The course will be under the direction of Alfred G. Knudson, Jr., M.D., Ph.D., Chairman of the Department of Pediatrics. For further information and registration, please write Julian Love, M.D., Director, School of Postgraduate Medicine, City of Hope Medical Center, Duarte, California.

Books

An Atlas of Cardiac Surgery. Jorge A. Rodriguez, M.D., Philadelphia, 1957, W. B. Saunders Co., 250 pages. Price $18.00.

The remarkable advances that have taken place in cardiac surgery in recent years are strikingly presented in this unusual Atlas. Dr. Rodriguez has presented the details of the operative technique of over a score of cardiac surgeons whose names are attached to the correction of some particular cardiac or vascular lesion. Thus the approach used by Bailey and by Harken for the correction of mitral stenosis, and those of Swan and of Scott for pulmonary stenosis. Some eighteen conditions are presented in this manner. Each has one or more large plates with drawings by the author depicting the various operative steps. The Atlas begins with an extensive discussion of the surgical anatomy of the heart and great vessels, with fifteen large plates of drawings made from dissections by the author. This is followed by a presentation of mechanical extracorporeal circulation by the machines developed by Gibbon, the Mayo Clinic, and the Minneapolis group. It is a book of operative techniques and hence of value to the surgeon rather than to the internist or pediatrician.

Endocrine Disorders in Childhood and Adolescence, ed. 2. Lawson Wilkins, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 526 pages. Price $17.50.

The first edition of Dr. Wilkins' book rapidly became the accepted standard text on the subject of endocrine disorders in childhood. In this second edition many changes have been made, together with some rearrangement of the material. The illustrations remain practically unchanged. In size it has increased from 382 to 526 pages, or by nearly 40 per cent. A number of the chapters have been rewritten and enlarged as the one on Diagnostic Methods: Hormone Assays and Tests. New chapters are included on the chemistry of the thyroid and adrenal functions. The chapter on the adrenogenital syndrome has been rewritten in view of the therapeutic results with cortisone and the discussion of hermaphroditism and gonadal dysgenesis to bring it abreast of the knowledge obtained in the last seven years. It is an extensively enlarged and revised "second edition" and the volume remains as one of the best monographs on the endocrine disorders that has appeared. We know of no other text on the subject that will be of as much help to the practitioner.

The Physiology and Biochemistry of Lactation. S. J. Folley, Springfield, Ill., 1957, Charles C Thomas, Publisher, 133 pages. Price $3.75.

A monograph by the head of the department of physiology at the National Institute for Research in Dairying at Shinfield, Berkshire. It summarizes our knowledge of lactation based on animal experimentation. Some of the theories of lactogenesis are discussed, and the studies on the biosynthesis of milk fat, protein, and lactose by the mammary gland. The book will be of value and interest to the physiologist and to those interested in milk secretion. It is not a text for the medical practitioner.

Editor's Column

STERILIZATION OF INSTRUMENTS FOR THE PREVENTION OF HEPATITIS

WHILE it is agreed that the virus of hepatitis can be destroyed by boiling in water, there are no published studies of the exact time necessary for the sterilization of instruments used in blood-letting by boiling or by the use of the autoclave. The U. S. Army recommendation is boiling for twenty minutes and that of the U. S. Public Health Service, fifteen minutes. The Expert Committee on Hepatitis of the WHO accepts ten minutes of boiling after thorough washing, steam under raised pressure, and dry heat at 170° C. for one-half hour if the temperature can be properly controlled, and, if not, 180° C. for one hour. The American Red Cross Blood Banks, which take many thousand pints of blood each month, avoid the danger of instrumental transmission by using disposable units of a needle attached to a polyethylene tube for each donor.

In April of this year the Department of Health of the City of New York issued a letter to all physicians and dentists in the city, recommending ten minutes' boiling in water for sterilization. This is also considered adequate by the Executive Committee of the Committee on Public Health of the New York Academy of Medicine.

According to statistics, hepatitis has been on the increase in recent years, although this in part may be due to better recognition and better reporting of cases of the infectious type of hepatitis. This type is commonly transmitted by direct contact and displays a tendency to occur in epidemic form. Epidemics can be readily checked by giving contacts prophylactic gamma globulin (0.01 c.c. per pound of body weight). During the incubation period and in the acute phase of infectious hepatitis, virus is present in the blood, so that transmission can occur by contaminated instruments, blood, or plasma. Gamma globulin is seemingly of no value in serum hepatitis, which may be transmitted only by transfusions of whole blood, plasma, or serum from an infected person, or by the use of insufficiently sterilized needles, syringes, or lancets used in blood-letting.

The specific recommendation of the New York City Department of Health is as follows:

"All needles, lancets and other piercing instruments, together with syringes or tubing connected to them, should be carefully washed to remove all foreign matter and then adequately sterilized. By adequate sterilization is meant autoclaving for 30 minutes at 250° F. (15 lb. pressure) or dry heat for 2 hours at 338° F., or boiling in water for 10 minutes."

PHYSICIANS' CHARGES AND THE COST OF LIVING

THE cost of medical care ranks high among the many complaints of today's high cost of living. One complaint frequently heard concerns the doctors' charges. While it is true that the cost of being sick has increased rapidly in the last ten years, how much of this is due to the increase in physicians' fees is a debatable matter.

First of all, the general increase in the cost of living must be taken into consideration. Going back some twenty years in order to obtain a basis for comparison, the cost of living index—food, rent, clothing, etc.—has more than doubled. This increase of a little over 100 per cent gives the dollar of today a purchasing power of only 50 cents compared with the dollar of 1937. About one-half of this increase took place in the postwar years 1945-1948, and only one-fourth in the last ten years. Thus while the cost of living has gone up in the last decade, the rate of the increase has been only a few percentage points each year compared with the rapid rise in the years immediately preceding.

As to doctors' charges: during these same years when the cost of living index was going up 101 per cent, doctors' charges increased only 78 per cent, according to Bureau of Labor statistics. The rate of increase for doctors' charges lagged considerably behind that of the cost of living index until 1950. Since then their rate of increase has been more rapid than that of the cost of living index, but as of 1957 the total percentage increase for doctors' charges is only a little more than three-fourths of what has happened to living costs. Hospital costs are a different story. These have almost quadrupled over the 1936 figures. While the cost of living has been going up 100 per cent, hospital costs have risen almost 300 per cent. Moreover, half of this increase has taken place since 1950, and two-thirds in the last ten years, while the cost of living index was leveling off.

Although there is no question but that the cost of illness has risen rapidly in recent years, it has not been due to an out-of-proportion increase in the doctors' charges. As a matter of fact, these charges have not kept pace with the rise in the cost of living over the past twenty years. Why hospital charges have gone up 300 per cent, as compared with a general cost of living increase of 101 per cent and one of 78 per cent in medical fees is a very complicated subject. Our point is simply that the doctor is not the villain in the act and that it is not an excessive increase in his charges that is responsible for the high cost of medical care today.